INVENTOR SEARCH

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=> fil capl; d que nos l39
FILE 'CAPLUS' ENTERED AT 08:07:05 ON 30 JUL 2009
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FILE COVERS 1907 - 30 Jul 2009  VOL 151 ISS 5
FILE LAST UPDATED: 29 Jul 2009  (20090729/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Jun 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Jun 2009

CAplus now includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2009.

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

The ALL, BIB, MAX, and STD display formats in the CA/CAplus family
of databases have been updated to include new citing references
information.  This enhancement may impact record import into
database management software.  For additional information, refer
to NEWS 22.
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


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L4          774 SEA FILE=REGISTRY SSS FUL L2
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L30        1366 SEA FILE=CAPLUS SPE=ON  ABB=ON  SHIMOMURA K?/AU
L31         387 SEA FILE=CAPLUS SPE=ON  ABB=ON  AONO H?/AU
L32         516 SEA FILE=CAPLUS SPE=ON  ABB=ON  TSUKAHARA Y?/AU
L33        2370 SEA FILE=CAPLUS SPE=ON  ABB=ON  HATA T?/AU
L34        1880 SEA FILE=CAPLUS SPE=ON  ABB=ON  L4
L39           1 SEA FILE=CAPLUS SPE=ON  ABB=ON  (L29 OR L30 OR L31 OR L32 OR
                L33) AND L34


=> d ibib abs hitstr l39

L39  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         2005:29228  CAPLUS  Full-text
DOCUMENT NUMBER:          142:107431
TITLE:                    Pain threshold fall inhibitor
```

INVENTOR(S): Shimomura, Kyoichi; Aono, Hiroyuki ; Tsukahara, Yaeko; Hata, Taeko
PATENT ASSIGNEE(S): Santen Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005002622	A1	20050113	WO 2004-JP9766	20040702
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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EP 1642590	A1	20060405	EP 2004-747234	20040702
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US 20070117853	A1	20070524	US 2005-562742	20051229 <--

PRIORITY APPLN. INFO.: JP 2003-270967 A 20030704
WO 2004-JP9766 W 20040702

OTHER SOURCE(S): MARPAT 142:107431

AB A medical drug capable of inhibiting the fall of pain threshold. In particular, a κ-opioid receptor agonist is capable of effectively inhibiting the fall of pain threshold, so that it is useful as a pain threshold fall inhibitor.

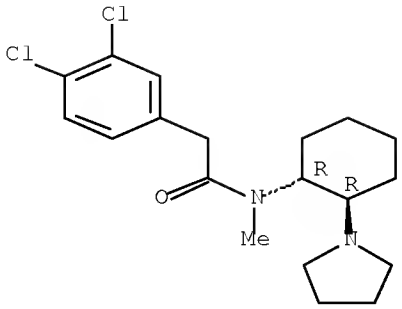
IT 83913-06-8 185951-07-9 610308-87-7
610308-92-4 610309-27-8 610309-63-2
823204-37-1 823204-39-3 823204-44-0
823204-46-2 823791-11-3,
2-(3,4-Dichlorophenyl)-N-methyl-N-[(5R',7S',8S')-7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acetamide methanesulfonate
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(κ-opioid receptor agonists as pain threshold fall inhibitors)

RN 83913-06-8 CAPLUS
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

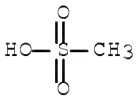
CRN 67198-13-4
CMF C19 H26 Cl2 N2 O

Relative stereochemistry.



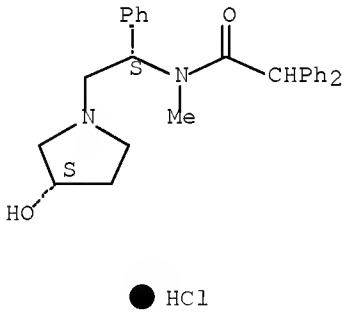
CM 2

CRN 75-75-2
CMF C H4 O3 S

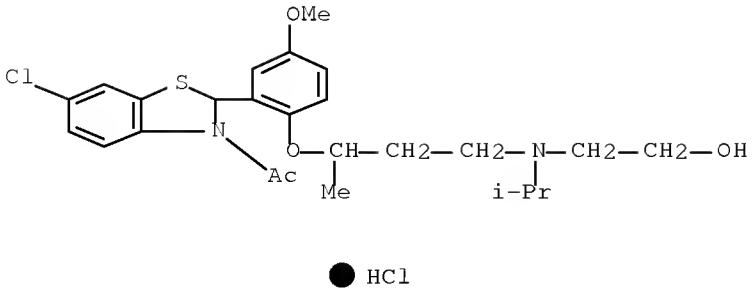


RN 185951-07-9 CAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.

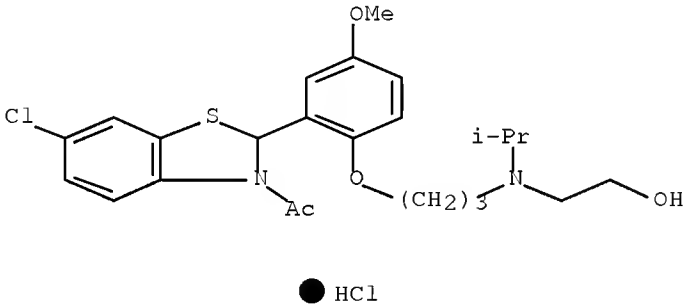


RN 610308-87-7 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-[3-[(2-hydroxyethyl)(1-methylethyl)amino]-1-methylpropoxy]-5-methoxyphenyl]-3(2H)-benzothiazolyl]-, hydrochloride (1:1) (CA INDEX NAME)



RN 610308-92-4 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-[3-[(2-hydroxyethyl)(1-methylethyl)amino]propoxy]-5-methoxyphenyl]-3(2H)-benzothiazolyl]-, hydrochloride (1:1), (+)- (CA INDEX NAME)

Rotation (+).



RN 610309-27-8 CAPLUS
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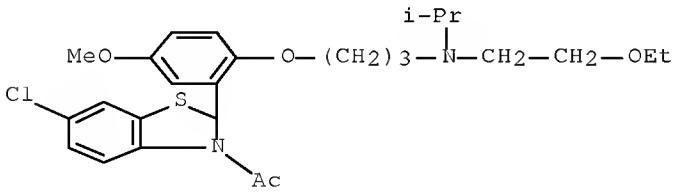
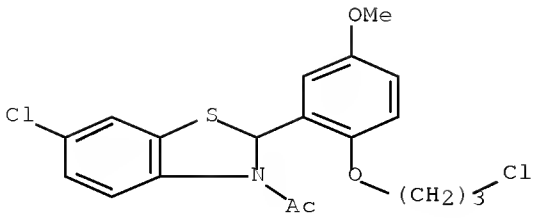


RN 610309-63-2 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-(3-chloropropoxy)-5-methoxyphenyl]-3(2H)-benzothiazolyl]-, (+)- (CA INDEX NAME)

Rotation (+).



RN 823204-37-1 CAPLUS
CN Butanedioic acid, 2,3-bis(acetyloxy)-, (2R,3R)-, compd. with 1-[6-chloro-2-[5-methoxy-2-[3-[(2-methoxyethyl)(1-methylethyl)amino]propoxy]phenyl]-3(2H)-benzothiazolyl]ethanone (1:2) (CA INDEX NAME)

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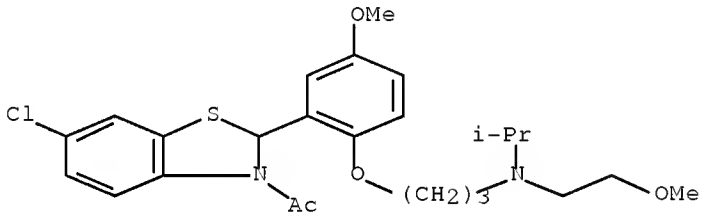
CRN 610309-32-5
CMF C25 H33 Cl N2 O4 S

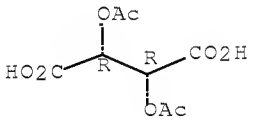
Rotation (+).



CM 2

CRN 51591-38-9
CMF C8 H10 O8

Absolute stereochemistry. Rotation (-).

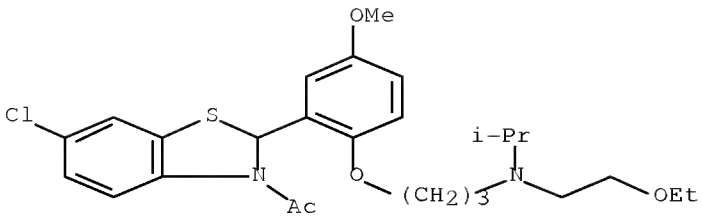


RN 823204-39-3 CAPLUS
CN Butanedioic acid, 2,3-bis(acetyloxy)-, (2R,3R)-, compd. with 1-[6-chloro-2-[2-[3-[(2-ethoxyethyl)(1-methylethyl)amino]propoxy]-5-methoxyphenyl]-3(2H)-benzothiazolyl]ethanone (1:2) (CA INDEX NAME)

CM 1

CRN 610309-34-7
CMF C26 H35 Cl N2 O4 S

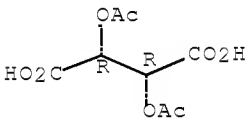
Rotation (+).



CM 2

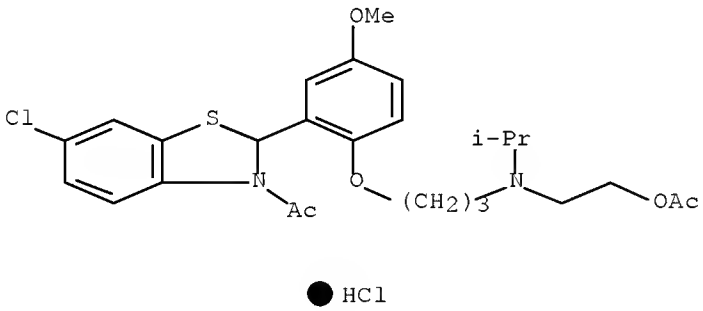
CRN 51591-38-9
CMF C8 H10 O8

Absolute stereochemistry. Rotation (-).



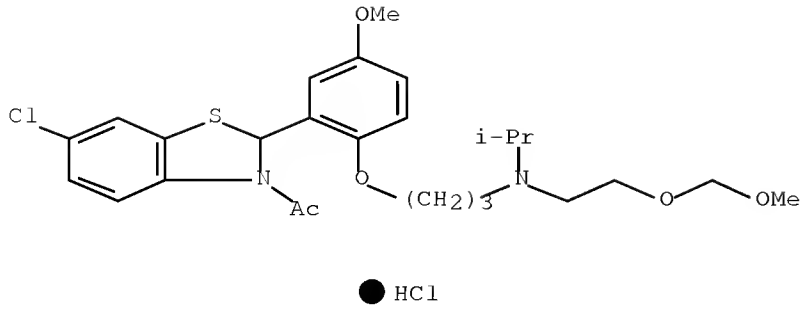
RN 823204-44-0 CAPLUS
CN Ethanone, 1-[2-[2-[3-[[2-(acetyloxy)ethyl](1-methylethyl)amino]propoxy]-5-methoxyphenyl]-6-chloro-3(2H)-benzothiazolyl]-, hydrochloride (1:1), (+)- (CA INDEX NAME)

Rotation (+).



RN 823204-46-2 CAPLUS
CN Ethanone, 1-[6-chloro-2-[5-methoxy-2-[3-[[2-(methoxymethoxy)ethyl](1-methylethyl)amino]propoxy]phenyl]-3(2H)-benzothiazolyl]-, hydrochloride (1:1), (+)- (CA INDEX NAME)

Rotation (+).

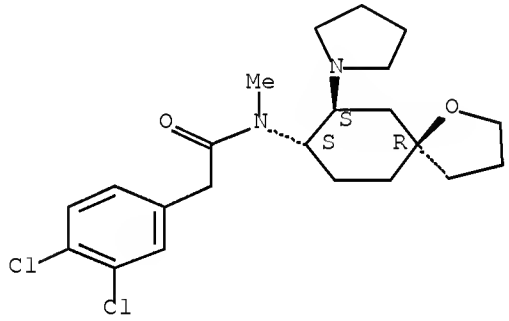


RN 823791-11-3 CAPLUS
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(5R,7S,8S)-7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

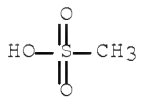
CRN 823791-10-2
CMF C22 H30 Cl2 N2 O2

Absolute stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

STRUCTURE SEARCH PART 1

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STRUCTURE FILE UPDATES:   28 JUL 2009  HIGHEST RN 1169929-67-2
DICTIONARY FILE UPDATES:  28 JUL 2009  HIGHEST RN 1169929-67-2

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http://www.cas.org/support/stngen/stndoc/properties.html
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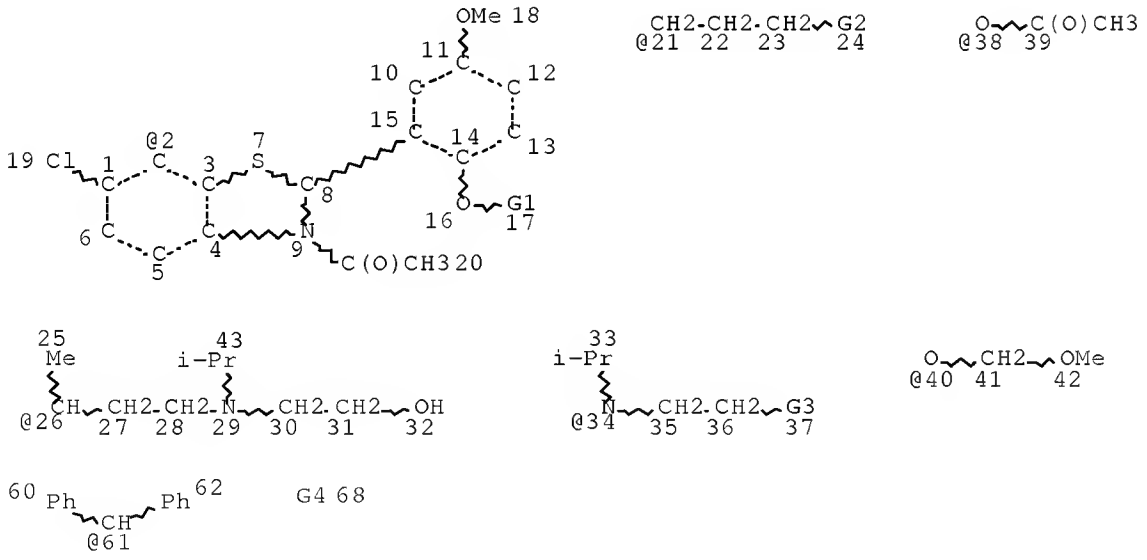

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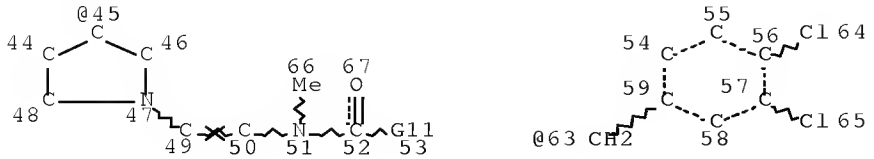

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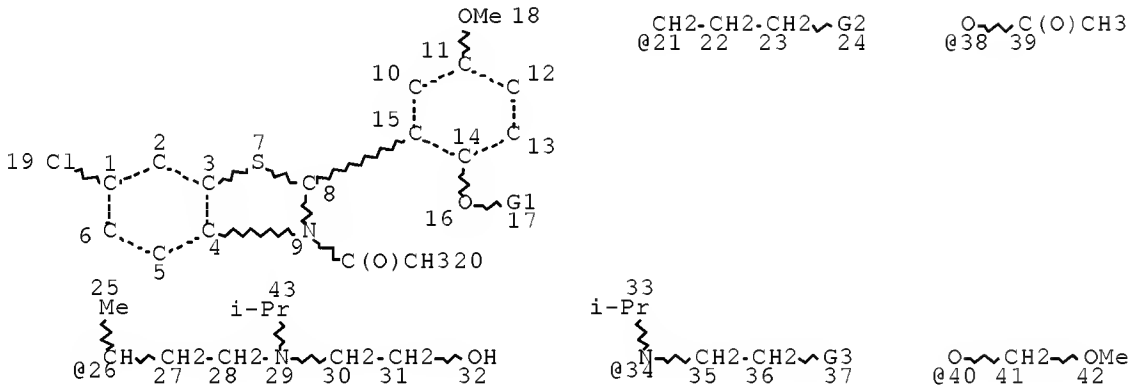

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STEREO ATTRIBUTES: NONE
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100.0% PROCESSED 33 ITERATIONS 33 ANSWERS
SEARCH TIME: 00.00.01

FILE 'CAPLUS' ENTERED AT 08:07:38 ON 30 JUL 2009
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FILE COVERS 1907 - 30 Jul 2009 VOL 151 ISS 5
FILE LAST UPDATED: 29 Jul 2009 (20090729/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2009

CAplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2009.

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This file contains CAS Registry Numbers for easy and accurate substance identification.

The ALL, BIB, MAX, and STD display formats in the CA/CAplus family of databases have been updated to include new citing references information. This enhancement may impact record import into database management software. For additional information, refer to NEWS 22.
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

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L35           3 SEA FILE=CAPLUS SPE=ON  ABB=ON  L10


L55           2 L35 NOT L39    L39=INVENTOR SEARCH ANSWER SET

=> d ibib abs hitstr l55 1-2

L55  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         2003:796678  CAPLUS  Full-text
DOCUMENT NUMBER:          139:312393
TITLE:                    κ-Opioid receptor agonist comprising
                          2-phenylbenzothiazoline derivative
INVENTOR(S):              Tokai, Maki; Honda, Takahiro; Niwa, Masashi; Osumi,
                          Yaeko; Fujimura, Ken-ichi; Kohno, Shin-ichi
PATENT ASSIGNEE(S):       Santen Pharmaceutical Co., Ltd., Japan
SOURCE:                   PCT Int. Appl., 129 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
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LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003082840	A1	20031009	WO 2003-JP3928	20030328
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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NZ 535987	A	20060831	NZ 2003-535987	20030328
CN 1911918	A	20070214	CN 2006-10139206	20030328
EP 2042173	A2	20090401	EP 2009-611	20030328
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US 7410987	B2	20080812		
JP 2009143940	A	20090702	JP 2009-21413	20090202
AU 2009201233	A1	20090423	AU 2009-201233	20090330

PRIORITY APPLN. INFO.:	JP 2002-97500	A	20020329
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	WO 2003-JP3928	W	20030328
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OTHER SOURCE(S): MARPAT 139:312393
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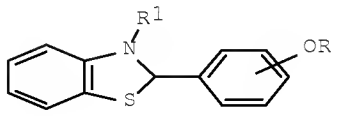

I

AB Dislocation closed is a κ-opioid receptor agonist comprising a 2-phenylbenzothiazoline derivative which is either a compound having a basic skeleton having a chemical structure represented by the general formula (I) (wherein R represents amino-substituted alkyl and R1 represents acyl) or a salt of the compound Also disclosed is an analgesic in particular for rheumatism-like diseases or anti-itching agent containing the above κ-opioid receptor agonist as an active ingredient. The presence of an amino-substituted alkyl group bonded to the Ph group of 2-phenylbenzothiazoline and the presence of an acyl group bonded to the nitrogen atom of the 2-phenylbenzothiazoline are important for the impartation of κ-opioid receptor agonistic activity. The compound I also possesses anti-nociception activity. For example, (+)-3-acetyl-6-chloro-2-[2-[3-[N-(2-ethoxyethyl)-N-isopropylamino]propoxy]- 5-methoxyphenyl]benzothiazoline hydrochloride at 30 mg/kg p.o. inhibited 100% pain in a mouse acetic acid-writhing assay.

IT 610308-21-9P 610308-47-9P 610308-60-6P
610308-87-7P 610308-88-8P 610308-91-3P
610308-92-4P 610308-93-5P 610309-04-1P
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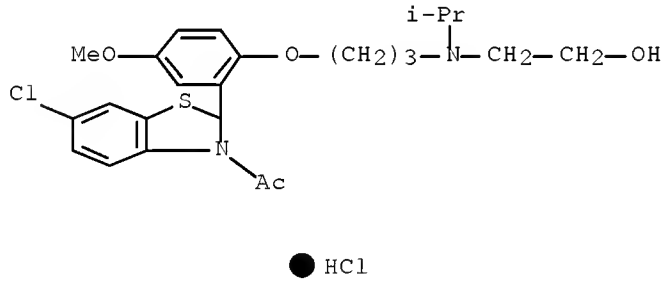
610309-30-3P 610309-32-5P 610309-33-6P
610309-34-7P 610309-42-7P 610309-45-0P
610309-46-1P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(κ-opioid receptor agonist, analgesic, and anti-itching agent comprising phenylbenzothiazoline derivative)

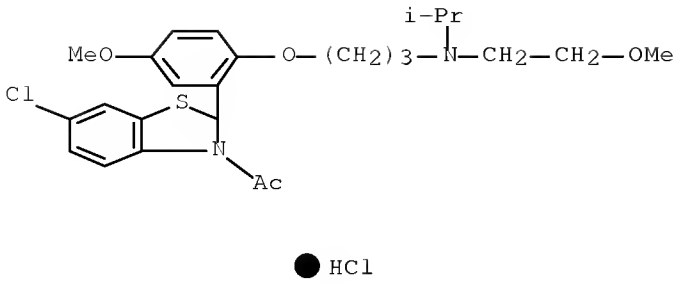
RN 610308-21-9 CAPLUS

CN Ethanone, 1-[6-chloro-2-[2-[3-[(2-hydroxyethyl)(1-methylethyl)amino]propoxy]-5-methoxyphenyl]-3(2H)-benzothiazolyl]-, hydrochloride (1:1) (CA INDEX NAME)

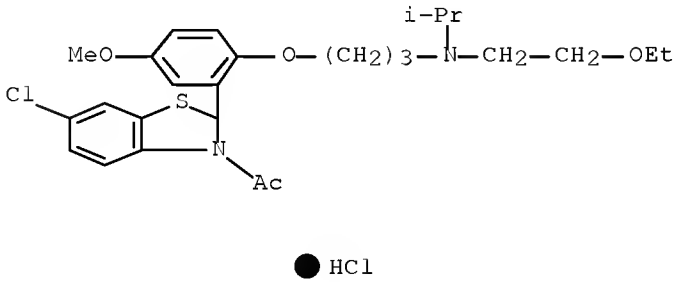


RN 610308-47-9 CAPLUS

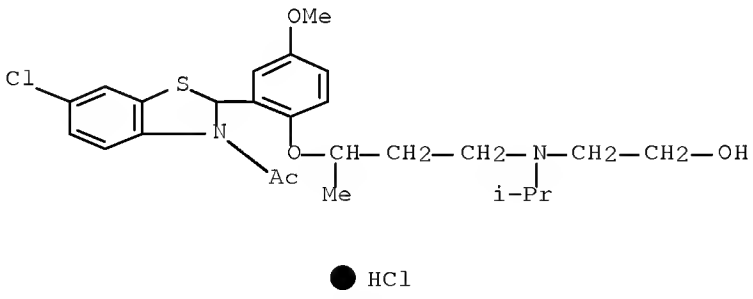
CN Ethanone, 1-[6-chloro-2-[5-methoxy-2-[3-[(2-methoxyethyl)(1-methylethyl)amino]propoxy]phenyl]-3(2H)-benzothiazolyl]-, hydrochloride (1:1) (CA INDEX NAME)



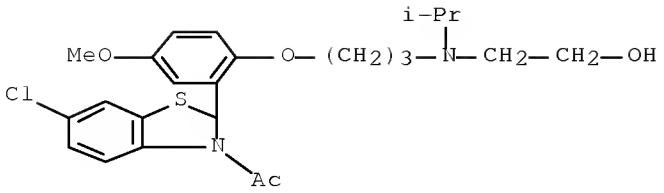
RN 610308-60-6 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-[3-[(2-ethoxyethyl)(1-methylethyl)amino]propoxy]-5-methoxyphenyl]-3(2H)-benzothiazolyl]-, hydrochloride (1:1) (CA INDEX NAME)



RN 610308-87-7 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-[3-[(2-hydroxyethyl)(1-methylethyl)amino]-1-methylpropoxy]-5-methoxyphenyl]-3(2H)-benzothiazolyl]-, hydrochloride (1:1) (CA INDEX NAME)

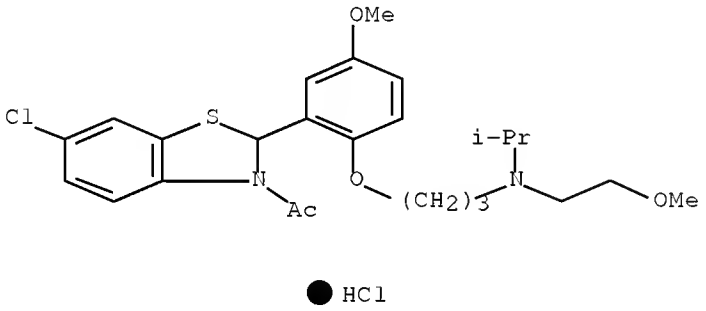


RN 610308-88-8 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-[3-[(2-hydroxyethyl)(1-methylethyl)amino]propoxy]-5-methoxyphenyl]-3(2H)-benzothiazolyl]- (CA INDEX NAME)



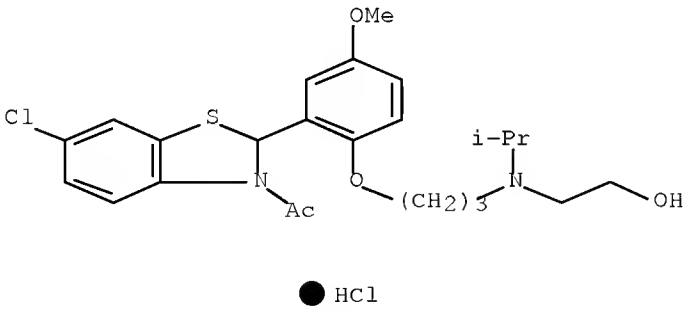
RN 610308-91-3 CAPLUS
CN Ethanone, 1-[6-chloro-2-[5-methoxy-2-[3-[(2-methoxyethyl)(1-methylethyl)amino]propoxy]phenyl]-3(2H)-benzothiazolyl]-, hydrochloride (1:1), (+)- (CA INDEX NAME)

Rotation (+).



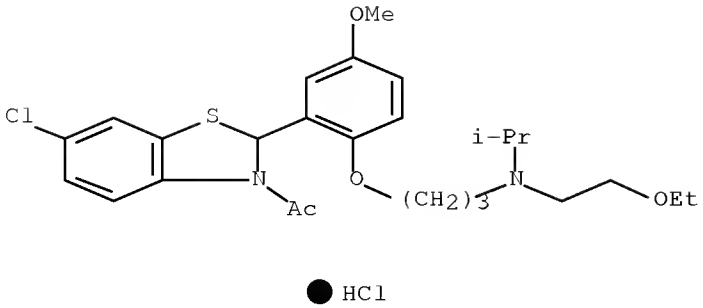
RN 610308-92-4 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-[3-[(2-hydroxyethyl)(1-methylethyl)amino]propoxy]-5-methoxyphenyl]-3(2H)-benzothiazolyl]-, hydrochloride (1:1), (+)- (CA INDEX NAME)

Rotation (+).



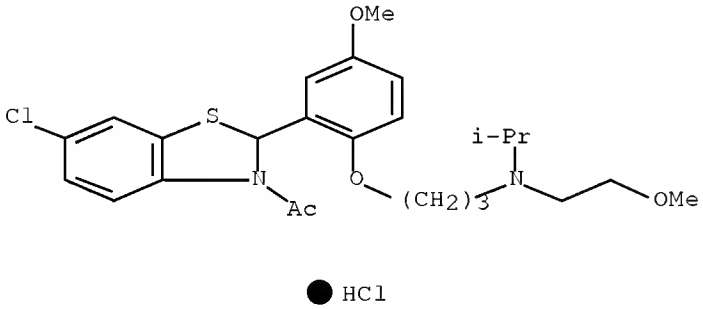
RN 610308-93-5 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-[3-[(2-ethoxyethyl)(1-methylethyl)amino]propoxy]-5-methoxyphenyl]-3(2H)-benzothiazolyl]-, hydrochloride (1:1), (+)- (CA INDEX NAME)

Rotation (+).



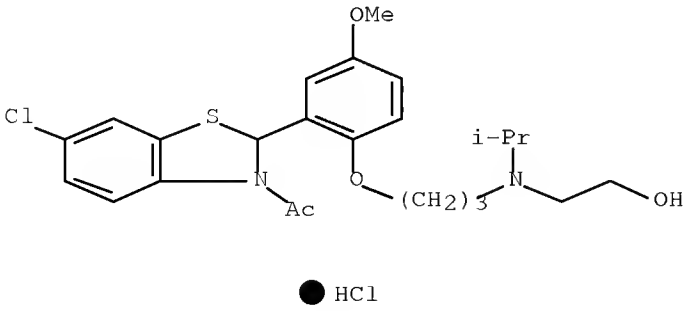
RN 610309-04-1 CAPLUS
CN Ethanone, 1-[6-chloro-2-[5-methoxy-2-[3-[(2-methoxyethyl)(1-methylethyl)amino]propoxy]phenyl]-3(2H)-benzothiazolyl]-, hydrochloride (1:1), (-)- (CA INDEX NAME)

Rotation (-).



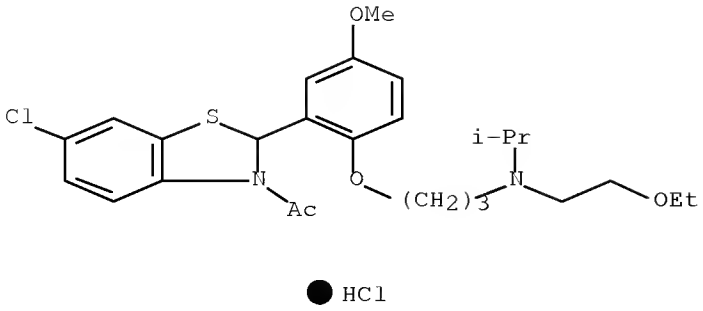
RN 610309-05-2 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-[3-[(2-hydroxyethyl)(1-methylethyl)amino]propoxy]-5-methoxyphenyl]-3(2H)-benzothiazolyl]-, hydrochloride (1:1), (-)- (CA INDEX NAME)

Rotation (-).

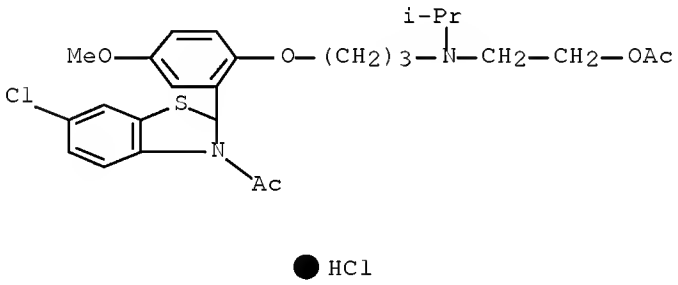


RN 610309-06-3 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-[3-[(2-ethoxyethyl)(1-methylethyl)amino]propoxy]-5-methoxyphenyl]-3(2H)-benzothiazolyl]-, hydrochloride (1:1), (-)- (CA INDEX NAME)

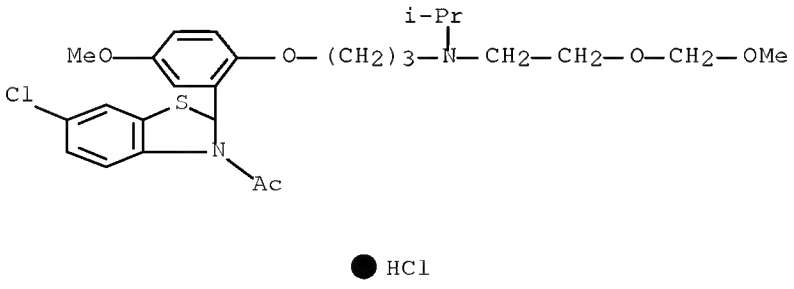
Rotation (-).



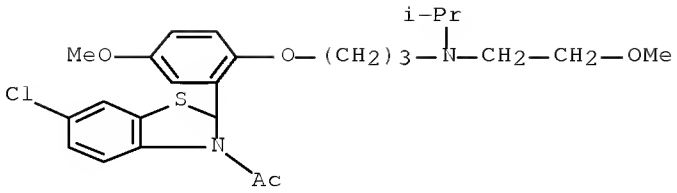
RN 610309-14-3 CAPLUS
CN Ethanone, 1-[2-[2-[3-[[2-(acetyloxy)ethyl](1-methylethyl)amino]propoxy]-5-methoxyphenyl]-6-chloro-3(2H)-benzothiazolyl]-, hydrochloride (1:1) (CA INDEX NAME)



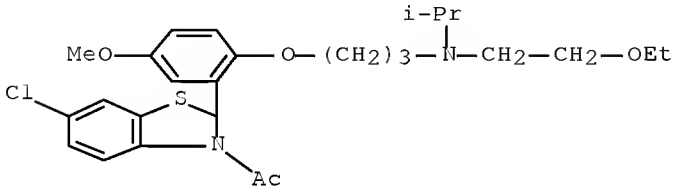
RN 610309-21-2 CAPLUS
CN Ethanone, 1-[6-chloro-2-[5-methoxy-2-[3-[[2-(methoxymethoxy)ethyl](1-methylethyl)amino]propoxy]phenyl]-3(2H)-benzothiazolyl]-, hydrochloride (1:1) (CA INDEX NAME)



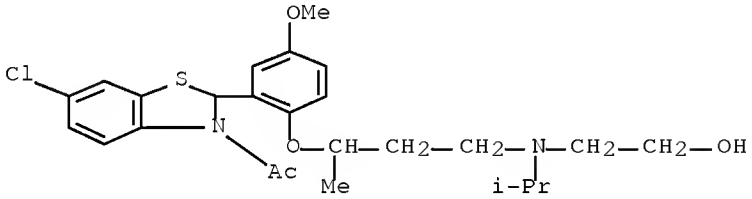
RN 610309-26-7 CAPLUS
CN Ethanone, 1-[6-chloro-2-[5-methoxy-2-[3-[(2-methoxyethyl)(1-methylethyl)amino]propoxy]phenyl]-3(2H)-benzothiazolyl]- (CA INDEX NAME)



RN 610309-27-8 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-[3-[(2-ethoxyethyl)(1-methylethyl)amino]propoxy]-5-methoxyphenyl]-3(2H)-benzothiazolyl]- (CA INDEX NAME)

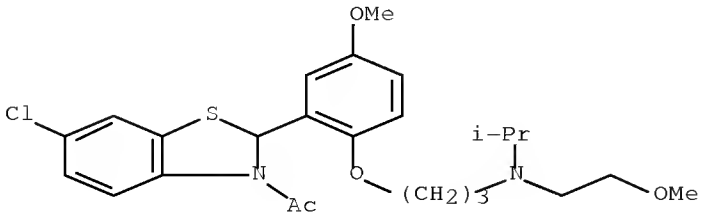


RN 610309-30-3 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-[3-[(2-hydroxyethyl)(1-methylethyl)amino]-1-methylpropoxy]-5-methoxyphenyl]-3(2H)-benzothiazolyl]- (CA INDEX NAME)



RN 610309-32-5 CAPLUS
CN Ethanone, 1-[6-chloro-2-[5-methoxy-2-[3-[(2-methoxyethyl)(1-methylethyl)amino]propoxy]phenyl]-3(2H)-benzothiazolyl]-, (+)- (CA INDEX NAME)

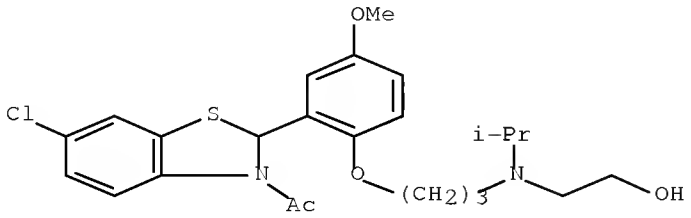
Rotation (+).



RN 610309-33-6 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-[3-[(2-hydroxyethyl)(1-

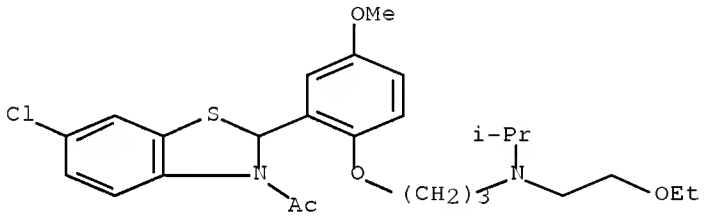
methylethyl)amino]propoxy]-5-methoxyphenyl]-3(2H)-benzothiazolyl]-, (+)-
(CA INDEX NAME)

Rotation (+).



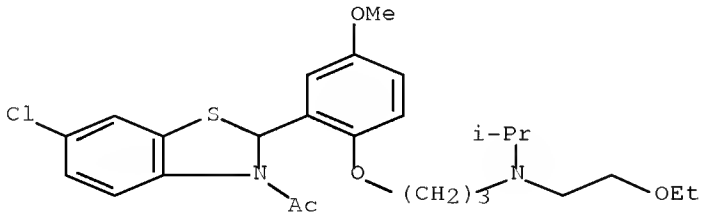
RN 610309-34-7 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-[3-[(2-ethoxyethyl)(1-
methylethyl)amino]propoxy]-5-methoxyphenyl]-3(2H)-benzothiazolyl]-, (+)-
(CA INDEX NAME)

Rotation (+).

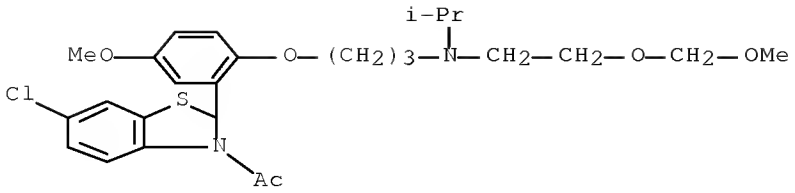


RN 610309-42-7 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-[3-[(2-ethoxyethyl)(1-
methylethyl)amino]propoxy]-5-methoxyphenyl]-3(2H)-benzothiazolyl]-, (-)-
(CA INDEX NAME)

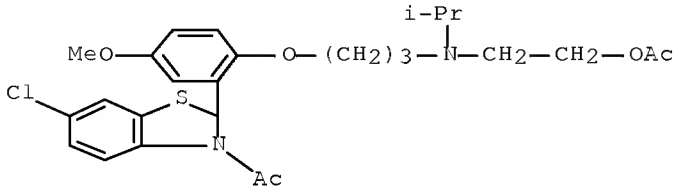
Rotation (-).



RN 610309-45-0 CAPLUS
CN Ethanone, 1-[6-chloro-2-[5-methoxy-2-[3-[[2-(methoxymethoxy)ethyl](1-
methylethyl)amino]propoxy]phenyl]-3(2H)-benzothiazolyl]- (CA INDEX NAME)

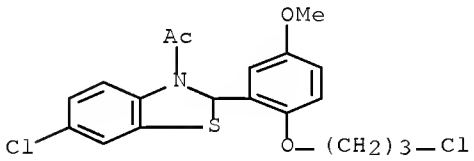


RN 610309-46-1 CAPLUS
CN Ethanone, 1-[2-[2-[3-[[2-(acetyloxy)ethyl](1-methylethyl)amino]propoxy]-5-methoxyphenyl]-6-chloro-3(2H)-benzothiazolyl]- (CA INDEX NAME)



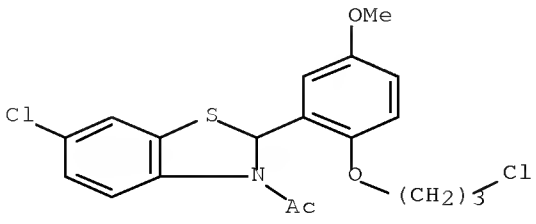
IT 113933-26-9P 610309-63-2P 610309-64-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(κ-opioid receptor agonist, analgesic, and anti-itching agent comprising phenylbenzothiazoline derivative)

RN 113933-26-9 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-(3-chloropropoxy)-5-methoxyphenyl]-3(2H)-benzothiazolyl]- (CA INDEX NAME)



RN 610309-63-2 CAPLUS
CN Ethanone, 1-[6-chloro-2-[2-(3-chloropropoxy)-5-methoxyphenyl]-3(2H)-benzothiazolyl]-, (+)- (CA INDEX NAME)

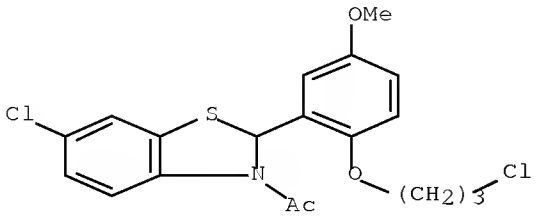
Rotation (+).



RN 610309-64-3 CAPLUS

CN Ethanone, 1-[6-chloro-2-[2-(3-chloropropoxy)-5-methoxyphenyl]-3(2H)-benzothiazolyl]-, (-)- (CA INDEX NAME)

Rotation (-).

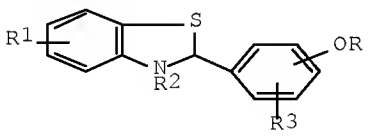


OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L55 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1988:167460 CAPLUS Full-text
DOCUMENT NUMBER: 108:167460
ORIGINAL REFERENCE NO.: 108:27533a,27536a
TITLE: Preparation of 2-phenylbenzothiazoline derivatives as cardiovascular agents
INVENTOR(S): Iwao, Junichi; Iso, Tadashi; Kawashima, Yoichi
PATENT ASSIGNEE(S): Santen Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 62221679	A	19870929	JP 1986-63189	19860319

PRIORITY APPLN. INFO.: JP 1986-63189 19860319
GI



I

AB The title compds. [I; R = AmR4; R1 = 1 or multiple groups selected from lower alkyl, lower alkoxy, OH, halo, cyano, NO2, lower haloalkyl, or lower alkanoyl; R2 = lower alkanoyl, lower alkylcarbamoyl, PhNHCO, MeSO2; R3 = 1 or multiple groups selected from H, OH, lower alkyl, lower alkoxy, NO2, halo, or lower alkanoyloxy; R4 = (CH)nR5, oxiranyl; R5 = N-substituted aminomethyl, halomethyl; m, n = 0, 1; A = C1-5 alkylene], useful as cardiovascular agents (no data) were prepared A solution of 2,5-(H2N)ClC6H3SH in PhMe was added to a solution of 2,5-(HO)(MeO)C6H3CHO in PhMe-MeOH and the mixture was heated at

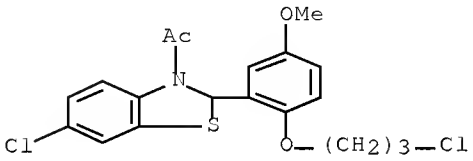
40° for 1 h. To the mixture, a solution of N-acetylimidazole in PhMe-MeOH was added and the mixture was stirred at room temperature for 6 h to give 53.3% I (OR = 2-OH, R1 = 6-Cl, R2 = Ac, R3 = 5-MeO).

IT 113933-26-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as cardiovascular agent)

RN 113933-26-9 CAPLUS

CN Ethanone, 1-[6-chloro-2-[2-(3-chloropropoxy)-5-methoxyphenyl]-3(2H)-benzothiazolyl]- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

STRUCTURE SEARCH PART 2

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=> fil reg; d stat que l41
FILE 'REGISTRY' ENTERED AT 08:08:01 ON 30 JUL 2009
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DICTIONARY FILE UPDATES:  28 JUL 2009  HIGHEST RN 1169929-67-2

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http://www.cas.org/support/stngen/stndoc/properties.html


L41           2 SEA FILE=REGISTRY SPE=ON  ABB=ON  823791-10-2 OR  823791-10-2/C
                RN


=> d ide l41 1-2

L41  ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2009 ACS on STN
RN   823791-11-3  REGISTRY
ED   Entered STN:  01 Feb 2005
CN   Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(5R,7S,8S)-7-(1-pyrrolidinyl)-1-
     oxaspiro[4.5]dec-8-yl]-, methanesulfonate (1:1)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(5R,7S,8S)-7-(1-pyrrolidinyl)-1-
     oxaspiro[4.5]dec-8-yl]-, monomethanesulfonate (9CI)
OTHER NAMES:
CN   2-(3,4-Dichlorophenyl)-N-methyl-N-[(5R',7S',8S')-7-(1-pyrrolidinyl)-1-
     oxaspiro[4.5]dec-8-yl]acetamide methanesulfonate
FS   STEREOSEARCH
MF   C22 H30 Cl2 N2 O2 . C H4 O3 S
SR   CA
LC   STN Files:   CA, CAPLUS, USPATFULL

     CM   1

     CRN  823791-10-2
     CMF  C22 H30 Cl2 N2 O2

Absolute stereochemistry.
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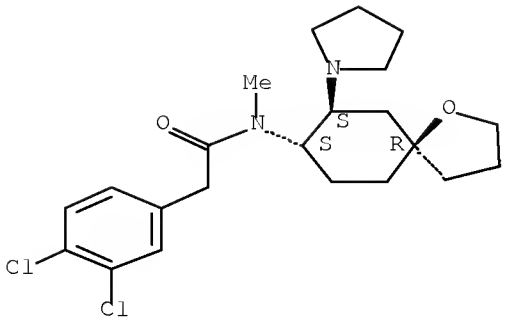
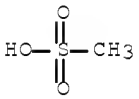


CM 2

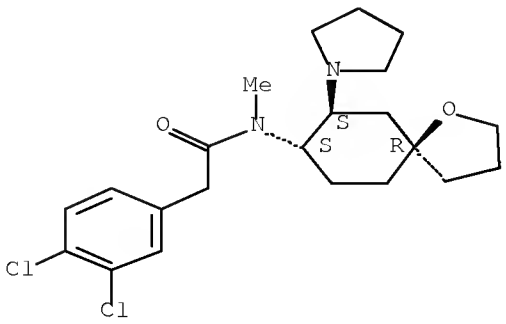
CRN 75-75-2
CMF C H4 O3 S



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L41 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2009 ACS on STN
RN 823791-10-2 REGISTRY
ED Entered STN: 01 Feb 2005
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(5R,7S,8S)-7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]- (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H30 Cl2 N2 O2
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.



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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

               1 REFERENCES IN FILE CA (1907 TO DATE)
               1 REFERENCES IN FILE CAPLUS (1907 TO DATE)


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FILE COVERS 1907 - 30 Jul 2009  VOL 151 ISS 5
FILE LAST UPDATED: 29 Jul 2009  (20090729/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Jun 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Jun 2009

CAplus now includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2009.

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information.  This enhancement may impact record import into
database management software.  For additional information, refer
to NEWS 22.
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


L41             2 SEA FILE=REGISTRY SPE=ON  ABB=ON  823791-10-2 OR  823791-10-2/C
                  RN
L48             2 SEA FILE=CAPLUS SPE=ON  ABB=ON  L41


=> s l48 not l39
L56             1 L48 NOT L39    L39=INVENTOR SEARCH ANSWER SET

=> d ibib abs hitind

L56  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         2008:1143815  CAPLUS  Full-text
DOCUMENT NUMBER:          150:182709
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TITLE: Chemical function-based pharmacophore development for novel, selective kappa opioid receptor agonists
AUTHOR(S): Singh, Nidhi; Nolan, Tammy L.; McCurdy, Christopher R.
CORPORATE SOURCE: Department of Medicinal Chemistry, Laboratory for Applied Drug Design and Synthesis, The University of Mississippi, MS, 38677, USA
SOURCE: Journal of Molecular Graphics & Modelling (2008), 27(2), 131-139
CODEN: JMGMFI; ISSN: 1093-3263
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In an effort to reduce or eliminate the centrally associated side effects produced by opioid analgesics there has been an interest in the preparation of peripherally acting opioid receptor agonists. These compds. would have very limited or no access to the central nervous system. As a first step towards developing peripheral kappa opioid receptor (KOP) agonists, the authors have developed a quant. predictive chemical function-based pharmacophore model of selective kappa opioid receptor agonists by using the HypoGen algorithm implemented in the Catalyst software. The input for HypoGen was a training set of 26 KOP agonists exhibiting K i values ranging between 0.015 nM and 2300 nM. The best output hypothesis consists of four features: one hydrophobic (HYD), one ring aromatic (RA), one hydrogen bond acceptor (HBA), and one pos. ionizable (PI) function. The predictive power of the model could be demonstrated by internal and external validation of the generated hypothesis. The resulting Catalyst pharmacophore can be used concurrently for rapid virtual screening of chemical databases to identify novel, selective KOP agonists that may be easily restricted to target tissues by synthetic modification. It is anticipated that such an approach will lead to the generation of novel selective KOP agonists that are clin. useful for the treatment of pain through peripheral mechanisms.
CC 1-3 (Pharmacology)
IT 67198-19-0 85888-40-0 96744-75-1 112217-76-2 114419-76-0
114419-79-3 115201-37-1 116508-24-8 126766-42-5 130497-34-6
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RL: BSU (Biological study, unclassified); BIOL (Biological study)
(chemical function-based pharmacophore development for novel, selective kappa opioid receptor agonists with possible analgesic applications)
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

STRUCTURE SEARCH PART 3

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FILE 'REGISTRY' ENTERED AT 08:08:54 ON 30 JUL 2009
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DICTIONARY FILE UPDATES:  28 JUL 2009  HIGHEST RN 1169929-67-2

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L45             2 SEA FILE=REGISTRY SPE=ON  ABB=ON  153205-46-0 OR 153205-46-0/CR
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FILE COVERS 1907 - 30 Jul 2009  VOL 151 ISS 5
FILE LAST UPDATED: 29 Jul 2009  (20090729/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Jun 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Jun 2009

CAplus now includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2009.

CAS Information Use Policies apply and are available at:
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http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate substance identification.

The ALL, BIB, MAX, and STD display formats in the CA/CAplus family of databases have been updated to include new citing references information. This enhancement may impact record import into database management software. For additional information, refer to NEWS 22.
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

L45 2 SEA FILE=REGISTRY SPE=ON ABB=ON 153205-46-0 OR 153205-46-0/CRN
L50 87 SEA FILE=CAPLUS SPE=ON ABB=ON L45

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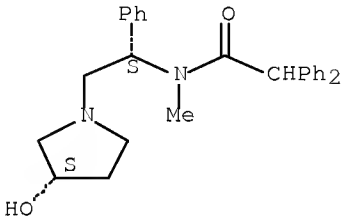
L50 ANSWER 74 OF 87 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1998:413024 CAPLUS Full-text
DOCUMENT NUMBER: 129:144659
ORIGINAL REFERENCE NO.: 129:29371a,29374a
TITLE: Effect of the peripherally selective κ-opioid agonist, asimadoline, on adjuvant arthritis
AUTHOR(S): Binder, Waltraud; Walker, Judith S.
CORPORATE SOURCE: School of Physiology and Pharmacology, University of New South Wales, Sydney, 2052, Australia
SOURCE: British Journal of Pharmacology (1998), 124(4), 647-654
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Opioids, though widely used as analgesics, have not been seriously considered as therapy for rheumatoid arthritis. The present study evaluated the dose-effect and time-dependence relationships of a new peripherally selective κ agonist, asimadoline, in rats with adjuvant arthritis. The arthritis was assessed by a pooled severity index combining the comprehensive criteria of edema, radiog. and histol. changes, in the hind limbs. Asimadoline was extremely effective in attenuating joint damage (by up to 80%) when administered parenterally (0.5 to 10 mg kg-1 day-1, i.p.) throughout the disease or during its early phase; treatment was less successful if confined to the latter stages. Ten fold higher doses were effective orally. Equimolar doses of a peripherally-selective antagonist, naloxone methiodide, and the κ-selective antagonist, MR2266, fully reversed the peripheral anti-arthritic effects of asimadoline (5 mg kg-1 day-1), indicating that asimadoline acts through peripheral κ-opioid receptors. However, an equivalent dose of MR2266 did not fully reverse the anti-arthritic effects of the highest dose of asimadoline (40 mg kg-1 day-1), suggesting a loss of κ-selectivity at this dose. Asimadoline also exhibited analgesic effects (mech. nociceptive thresholds) in arthritic but not non-arthritic rats, indicating that inflammation is necessary for asimadoline-induced analgesia. These data confirm our previous findings that κ-opioids possess anti-arthritic properties and that these effects are mediated via peripheral κ-receptors. The present results are new in showing that the peripherally acting κ-opioid agonist, asimadoline, is a potent anti-arthritic agent. Such novel drugs, essentially lacking central side effects, herald new treatments for rheumatoid arthritis.

IT 153205-46-0, Asimadoline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(κ-opioid agonist asimadoline effect on adjuvant arthritis)
RN 153205-46-0 CAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (CA INDEX NAME)

Absolute stereochemistry.



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L50 ANSWER 75 OF 87 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1998:397785 CAPLUS Full-text
DOCUMENT NUMBER: 129:67799
ORIGINAL REFERENCE NO.: 129:14075a,14078a
TITLE: Preparation of 1,4-diacyl-2-(pyrrolidinomethyl)piperazines and analogs as kappa opioid receptor agonists
INVENTOR(S): Kruse, Lawrence I.; Chang, An-Chih; DeHaven-Hudkins, Diane L.; Farrar, John J.; Gaul, Forrest; Kumar, Virendra; Marella, Michael Anthony; Maycock, Alan L.; Zhang, Wei Yuan
PATENT ASSIGNEE(S): Adolor Corp., USA
SOURCE: U.S., 67 pp., Cont.-in-part of U. S. 5,688,955. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

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US 5646151	A	19970708	US 1996-612680	19960308
US 5688955	A	19971118	US 1997-796078	19970205
US 5981513	A	19991109	US 1998-45522	19980321
CA 2289055	A1	19990128	CA 1998-2289055	19980619
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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,

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JP 2001510154		T	20010731	JP 2000-502767	19980619
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ZA 9806208		A	19990125	ZA 1998-6208	19980713
US 6028063		A	20000222	US 1999-307517	19990507
US 6180623		B1	20010130	US 1999-436057	19991108
NO 9906352		A	20000313	NO 1999-6352	19991220
US 20020042399		A1	20020411	US 2001-769450	20010126
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				US 1999-307517	A3 19990507
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OTHER SOURCE(S): MARPAT 129:67799

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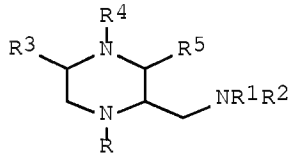


I

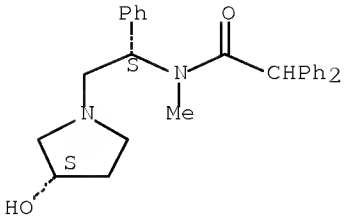
AB Title compds. [I; R = CO(CH2)nR6; R1,R2 = Me; R1R2 = (CH2)m, CH2CH(OH)CH2, CH2CH2OCH2CH2, etc.; R3,R5 = CH2NHSO2Me, CH2NHP(O)(OH)2, CH2OP(O)(OH)2, etc.; R4 = P(O)(OH)2, (CH2)pCO2H, CO2Me, etc.; R6 = (un)substituted (hetero)aryl; m = 4-8; n = 1-3; p = 0-20] were prepared for treatment of pruritus. Thus, (R)-I (R = COCH2C6H3Cl2-3,4, NR1R2 = pyrrolidino, R3 = R5 = H, R4 = SO2Me) was prepared Data for biol. activity of I were given.

IT 153205-46-0
RL: PRPH (Prophetic)
(Preparation of 1,4-diacyl-2-(pyrrolidinomethyl)piperazines and analogs as kappa opioid receptor agonists)

RN 153205-46-0 CAPLUS

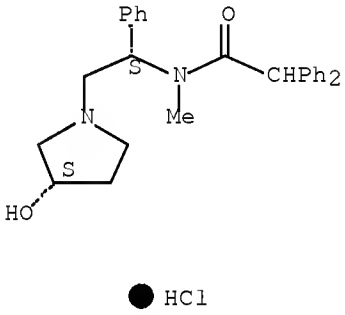
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (CA INDEX NAME)

Absolute stereochemistry.



IT 185951-07-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 1,4-diacyl-2-(pyrrolidinomethyl)piperazines and analogs as kappa opioid receptor agonists)
RN 185951-07-9 CAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L50 ANSWER 76 OF 87 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1998:319400 CAPLUS Full-text
DOCUMENT NUMBER: 129:62858
ORIGINAL REFERENCE NO.: 129:12885a,12888a
TITLE: Effects of kappa-opioid receptor agonists on responses to colorectal distension in rats with and without acute colonic inflammation
AUTHOR(S): Burton, Maureen B.; Gebhart, G. F.
CORPORATE SOURCE: Department of Pharmacology, College of Medicine, The University of Iowa, Iowa City, IA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1998), 285(2), 707-715
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The objective of this study was to evaluate the effects of kappa-opioid receptor agonists on pressor and visceromotor responses to colorectal distension in awake, unrestrained rats, a model of visceral pain. Because

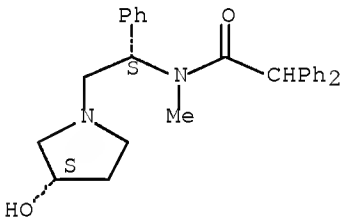
visceral pain can be enhanced in the presence of inflammation, the study was conducted in rats that had been given either intracolonic saline or 5% acetic acid 6 h before drug administration. We developed a method of staircase colorectal distension as a means of obtaining stimulus-response functions over a short period of time. Kappa-opioid receptor agonists, given i.v. in a cumulative dose paradigm, dose-dependently attenuated both the pressor and visceromotor responses to colorectal distension. In addition, all drugs tested also increased response threshold. The rank order of potency of the drugs tested was: C1977 > U69,593 > U50,488 ≥ morphine ≥ EMD61,753 > ICI204,448. EDs of these drugs were antagonized by naloxone, but not by either of two kappa-opioid receptor-selective antagonists (nor-binaltorphimine and 2-(3,4-dichlorophenyl)-N-methyl-N-(1-[3-isothiocyanate phenyl]-2-[1-pyrrolidinyl]ethyl)-acetamide). Acute inflammation of the colon did not lead to changes in the potency of the agonists tested. The present results provide further evidence that kappa-opioid receptor agonists significantly attenuate visceral nociception and, in conjunction with other information, suggest that a peripherally restricted kappa-opioid receptor agonist would be therapeutically effective in relieving visceral pain.

IT 153205-46-0, EMD61753
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(kappa-opioid receptor agonists significantly attenuate visceral nociception)

RN 153205-46-0 CAPLUS

CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 50 THERE ARE 50 CAPLUS RECORDS THAT CITE THIS RECORD (50 CITINGS)

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L50 ANSWER 77 OF 87 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1998:89564 CAPLUS Full-text

DOCUMENT NUMBER: 128:136113

ORIGINAL REFERENCE NO.: 128:26595a,26598a

TITLE: Brain concentrations of asimadoline in mice. The influence of coadministration of various P-glycoprotein substrates

AUTHOR(S): Bender, H. M.; Dasenbrock, J.

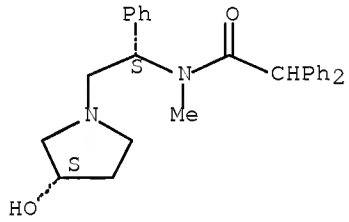
CORPORATE SOURCE: Inst. Pharmacokinetics Metabolism, Merck K.-G.a.A., Grafing, D-85567, Germany

SOURCE: International Journal of Clinical Pharmacology and Therapeutics (1998), 36(2), 76-79
CODEN: ICTHEK; ISSN: 0946-1965

PUBLISHER: Dustri-Verlag Dr. Karl Feistle

DOCUMENT TYPE: Journal
LANGUAGE: English
AB The influence of the P-glycoprotein (Pgp) substrates digoxin, ondansetron, cyclosporin A, vinblastine, and dexamethasone on brain concns. of asimadoline, a peripherally selective .vkappa.-opioid agonist and Pgp substrate, was investigated in mice. Due to a plateau phase of brain concns. (radioactivity and parent drug) 15-30 min after administration, the time schedule above was chosen for coadministration of asimadoline and Pgp substrates. In the brain, concns. of parent drug and radioactivity showed no differences when coadministered with Pgp substrates. Thus, an influence of coadministered Pgp substrates on the brain concentration of asimadoline is unlikely.
IT 153205-46-0, Asimadoline
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(brain concns. of asimadoline in mice. The influence of coadministration of various P-glycoprotein substrates)
RN 153205-46-0 CAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)

L50 ANSWER 78 OF 87 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1997:752779 CAPLUS Full-text
DOCUMENT NUMBER: 128:34783
ORIGINAL REFERENCE NO.: 128:6857a,6860a
TITLE: Kappa agonist compounds (acylpiperazines and analogs) and pharmaceutical formulations thereof
INVENTOR(S): Kruse, Lawrence I.; Chang, An-chih; Dehaven-Hudkins, Diane L.; Farrar, John J.; Gaul, Forrest; Kumar, Virendra; Marella, Michael Anthony; Maycock, Alan L.; Zhang, Wei Yuan
PATENT ASSIGNEE(S): Adolor Corp., USA
SOURCE: U.S., 65 pp., Cont.-in-part of U.S. Ser. No. 612,680.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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US 6054445	A	20000425	US 1999-307387		19990507
US 6239154	B1	20010529	US 1999-372191		19990811
US 6180623	B1	20010130	US 1999-436057		19991108
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US 20030144272	A1	20030731	US 2002-146693		20020515
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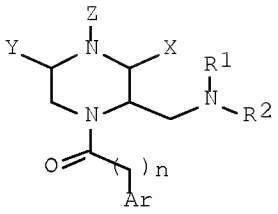
			US 1998-45522	A3	19980321
			US 1998-150369	A2	19980909
			US 1998-183011	A3	19981030
			US 1999-307517	A3	19990507
			US 1999-372191	A3	19990811
			US 1999-436057	A1	19991108
			US 2000-478482	A2	20000106
			US 2001-769450	A3	20010126
			US 2002-146693	A1	20020515

OTHER SOURCE(S): MARPAT 128:34783
GI



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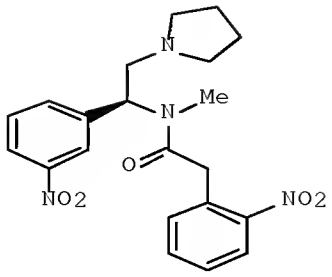


II

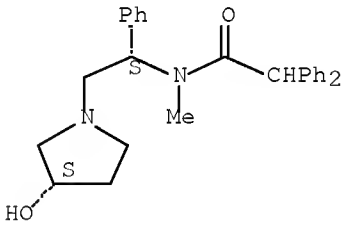
AB Compds. having kappa opioid agonist activity, compns. containing them, and methods of using them as analgesics are provided. The compds. have 4 general structures, e.g., I [n = 1-3; R1 = R2 = Me; or NR1R2 forms various cyclic systems; Ar = (un)substituted Ph, benzothienyl, benzofuranyl, naphthyl, CHPh2, or 9-fluorenyl; Z = wide variety of sidechains; X, Y = various derivs. of CH2OH and CH2NH2]. A large number of compds., as HCl salts and/or free bases, were prepared, tested, and/or claimed. For instance, title compound II.HCl, i.e. ADL-01-0115-4, was prepared in 51% yield by amidation of 2-nitrophenylacetic acid with the corresponding secondary amine using DCC and pyridine in CH2Cl2. In tests for displacement of [3H]-diprenorphin or [3H]-U-69593 from kappa receptors in vitro, II.HCl had Ki values of 35 and 3.2 nM, resp.

IT 185951-07-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of acylpiperazines and analogs as kappa agonists)

RN 185951-07-9 CAPLUS

CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

OS.CITING REF COUNT: 54 THERE ARE 54 CAPLUS RECORDS THAT CITE THIS RECORD (54 CITINGS)

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L50 ANSWER 79 OF 87 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1997:706772 CAPLUS Full-text

DOCUMENT NUMBER: 128:18278

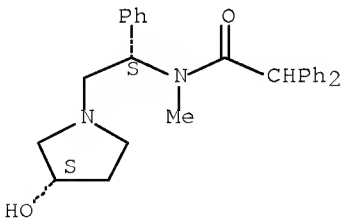
ORIGINAL REFERENCE NO.: 128:3435a,3438a

TITLE: Novel developments with selective, non-peptidic kappa-opioid receptor agonists
AUTHOR(S): Barber, Andrew; Gottschlich, Rudolf
CORPORATE SOURCE: Department of CNS Research, Preclinical Pharmaceutical Research, Merck KGaA, Darmstadt, 64271, Germany
SOURCE: Expert Opinion on Investigational Drugs (1997), 6(10), 1351-1368
CODEN: EOIDER; ISSN: 0967-8298
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 136 refs. Despite the recent introduction of a number of new compds., there has of late been a cooling of interest by pharmaceutical companies in the development of centrally-active, selective kappa opioid agonists for therapeutic purposes. This is reflected in the discontinuation of a number of clin. trials, for reasons that are often not completely clear to outside observers. Spiradoline and enadoline have apparently been abandoned as potential analgesics because they induce dose-limiting central side-effects (i.e., dysphoria) in models of post-surgical pain. The development of niravoline as an aquaretic for the treatment of cirrhosis with ascites and other hyponatremic disorders has also been halted. Enadoline may yet find some application against ischemic stroke and severe head injury, presumably in comatose patients in whom psychiatric side-effects are taken to be immaterial, while apadoline and TRK 820 remain in Phase II clin. testing against cancer pain. The peripherally-selective kappa agonists, asimadoline, and the atypical compound, fedotozine, are well-tolerated in man. Results of Phase III trials of fedotozine against irritable bowel syndrome and dyspepsia have, however, ultimately been disappointing, whereas asimadoline is currently in Phase II clin. trials against pain of rheumatic and osteoarthritic origin. The results of these trials are eagerly awaited.

IT 153205-46-0, Asimadoline
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel developments with selective, non-peptidic kappa-opioid receptor agonists as analgesics)
RN 153205-46-0 CAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 43 THERE ARE 43 CAPLUS RECORDS THAT CITE THIS RECORD (44 CITINGS)
REFERENCE COUNT: 137 THERE ARE 137 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L50 ANSWER 80 OF 87 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1997:231063 CAPLUS Full-text

DOCUMENT NUMBER: 126:216665
ORIGINAL REFERENCE NO.: 126:41815a,41818a
TITLE: Thermostable form of EMD-61753
INVENTOR(S): Stein, Inge; Beeres, Holger; Beschmann, Klaus; Neuenfeld, Steffen
PATENT ASSIGNEE(S): Merck Patent Gmbh, Germany
SOURCE: Ger. Offen., 5 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19531464	A1	19970227	DE 1995-19531464	19950826
EP 761650	A1	19970312	EP 1996-112489	19960802
EP 761650	B1	20011031		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
AT 207895	T	20011115	AT 1996-112489	19960802
ES 2165948	T3	20020401	ES 1996-112489	19960802
CZ 287783	B6	20010214	CZ 1996-2434	19960816
AU 9662149	A	19970306	AU 1996-62149	19960819
AU 716615	B2	20000302		
IN 1996CA01481	A	20050304	IN 1996-CA1481	19960820
JP 09110830	A	19970428	JP 1996-221296	19960822
SK 282437	B6	20020205	SK 1996-1089	19960822
CA 2184049	A1	19970227	CA 1996-2184049	19960823
CA 2184049	C	20071002		
NO 9603526	A	19970227	NO 1996-3526	19960823
NO 307048	B1	20000131		
ZA 9607200	A	19970303	ZA 1996-7200	19960823
CN 1151986	A	19970618	CN 1996-111404	19960823
CN 1081631	C	20020327		
BR 9603540	A	19980512	BR 1996-3540	19960823
RU 2174976	C2	20011020	RU 1996-116925	19960823
TW 513407	B	20021211	TW 1996-85110305	19960823
PL 187691	B1	20040930	PL 1996-315799	19960823
HU 9602346	A2	19970929	HU 1996-2346	19960826
HU 9602346	A3	19980128		
HU 226667	B1	20090629		
US 6060504	A	20000509	US 1996-703350	19960826
JP 2009046501	A	20090305	JP 2008-257423	20081002

PRIORITY APPLN. INFO.: DE 1995-19531464 A 19950826
JP 1996-221296 A3 19960822

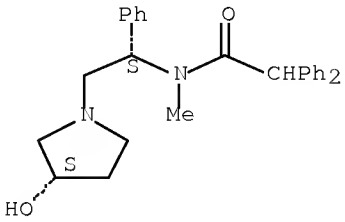
OTHER SOURCE(S): CASREACT 126:216665

AB N-methyl-N-[(1S)-1-phenyl-2-[(3S)-3-hydroxypyrrolidin-1-yl]ethyl]-2,2-diphenylacetamide (EMD-61753), a κ-opioid antagonist for treatment of inflammatory bowel disease, hyperalgesia, burns, neurodermatitis, and rheumatic disorders, is prepared in a highly thermostable crystalline modification designated type IV (m. 220-225°) by condensation of 1-[(1S)-3-hydroxypyrrolidin-1-yl]-(2S)-2-methylamino-2-phenylethane with diphenylacetyl chloride at low temperature (preferably 0-8°). Type IV is also formed during prolonged storage of type II at 170°, or by rapid cooling of a melt of type II from >200° and storage at room temperature for 12-16 h. Prepns. containing EMD-61753 type IV can be sterilized. Thus, suppositories were prepared from a melt of EMD-61753 20, soybean lecithin 100, and cocoa butter 1400 g.

IT 153205-46-0P, EMD-61753
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses)
(thermostable form of EMD-61753)
RN 153205-46-0 CAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

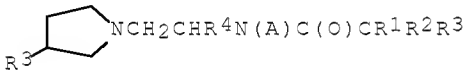
L50 ANSWER 81 OF 87 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1997:97208 CAPLUS Full-text
DOCUMENT NUMBER: 126:108937
ORIGINAL REFERENCE NO.: 126:20967a,20970a
TITLE: N-(pyrrolidinoethyl)arylacetamides as κ-opiate agonists for treatment of inflammatory bowel disease
INVENTOR(S): Barber, Andrew; Seyfried, Christoph; Bartoszyk, Gerd; Gottschlich, Rudolf
PATENT ASSIGNEE(S): Merck Patent Gmbh, Germany
SOURCE: Ger. Offen., 7 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19523502	A1	19970102	DE 1995-19523502	19950628
EP 752246	A2	19970108	EP 1996-109915	19960620
EP 752246	A3	19970226		
EP 752246	B1	20020313		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
AT 214275	T	20020315	AT 1996-109915	19960620
ES 2171577	T3	20020916	ES 1996-109915	19960620
IN 1996CA01158	A	20050930	IN 1996-CA1158	19960621
AU 9656162	A	19970109	AU 1996-56162	19960624
AU 708699	B2	19990812		
CZ 289805	B6	20020417	CZ 1996-1866	19960625
CA 2179955	A1	19961229	CA 1996-2179955	19960626
CA 2179955	C	20081007		
JP 09020659	A	19970121	JP 1996-165988	19960626
RU 2190401	C2	20021010	RU 1996-112771	19960626
NO 9602720	A	19961230	NO 1996-2720	19960627
NO 309674	B1	20010312		
ZA 9605480	A	19970127	ZA 1996-5480	19960627
CN 1145781	A	19970326	CN 1996-110142	19960627
CN 1119147	C	20030827		

BR 9602915	A	19980422	BR 1996-2915		19960627
US 5776972	A	19980707	US 1996-671502		19960627
TW 430557	B	20010421	TW 1996-85107762		19960627
PL 185537	B1	20030530	PL 1996-314996		19960627
SK 283497	B6	20030805	SK 1996-843		19960627
HU 9601798	A1	19980330	HU 1996-1798		19960628
US 5977161	A	19991102	US 1998-27228		19980220
JP 2008201794	A	20080904	JP 2008-112917		20080423
PRIORITY APPLN. INFO.:			DE 1995-19523502	A	19950628
			JP 1996-165988	A3	19960626
			US 1996-671502	A3	19960627

OTHER SOURCE(S): MARPAT 126:108937

GI



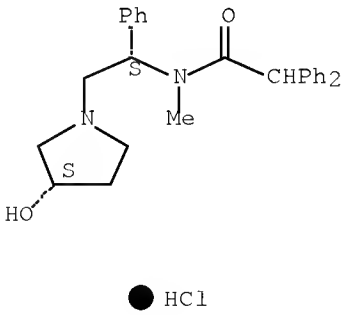
I

AB The title compds. [I; R1 = aryl, C3-7 cycloalkyl, C4-8 cycloalkylalkyl; R2 = aryl; R3 = H, OH, alkyl, alkoxy; R4 = alkyl, (substituted) Ph; R5 = OH, CH2OH; A = C1-7 alkyl] and their salts and glycosylated derivs. are useful in treatment of inflammatory bowel disease to relieve pain and restore normal bowel motility, as well as in treatment of ileus and neurodermitis. Thus, tablets containing 10 mg I were prepared from a mixture containing I 1, lactose 4, potato starch 1.2, talc 0.2, and Mg stearate 0.1 kg.

IT 185951-07-9 185951-07-9D, glycosylated derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(N-(pyrrolidinoethyl)arylacetamides as κ-opiate agonists for treatment of inflammatory bowel disease)

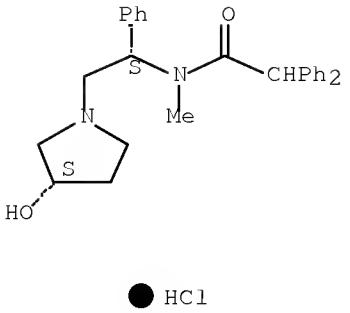
RN 185951-07-9 CAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.



RN 185951-07-9 CAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl-, hydrochloride (1:1) (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)

L50 ANSWER 82 OF 87 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1996:411968 CAPLUS Full-text
DOCUMENT NUMBER: 125:104282
ORIGINAL REFERENCE NO.: 125:19227a,19230a
TITLE: Search for the pharmacophore in kappa-agonistic diazabicyclo[3.3.1]nonan-9-one-1,5-diesters and arylacetamides
AUTHOR(S): Brandt, Wolfgang; Drosihn, Susanne; Haurand, Michael; Holzgrabe, Ulrike; Nachtsheim, Corina
CORPORATE SOURCE: Pharm. Inst., Univ. bonn, Bonn, 53115, Germany
SOURCE: Archiv der Pharmazie (Weinheim, Germany) (1996), 329(6), 311-323
CODEN: ARPMAS; ISSN: 0365-6233
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Several heterocyclic bicyclo[3.3.1]nonan-9-ones were found to have a high affinity to κ opioid receptors. 3,7-Diazabicyclononanones with 2,4-dipyridyl side chains were the most potent agonists whereas the corresponding 3-oxa-7-azabicyclo[3.3.1]nonan-9-one and compds. with Ph substituents in 2 and 4 position are almost inactive. The purpose of this study was to unravel the active conformation of the bicyclononanones using well-known κ-selective agonists such as ketocyclacocine, arylacetamides, several isoquinolines, CI-977, and four stereoisomers of EMD-61753 for comparison. In order to determine the geometry of the diazabicycles in solution pH-dependent NMR measurements of the bicycles were recorded and the results were related to the geometries of the aforementioned κ agonists obtained from semiempirical PM3 calcns. A chair-boat conformation and a protonation at the N7 nitrogen atom of the diazabicyclononanones were found to be the pharmacophoric conformation. Comparison of the spatial arrangements, electrostatic, hydrophobic, and hydrogen bonding potentials of all κ-selective agonists led to a model of structure-activity relationships of ligands of the κ receptor. The arrangement of the pharmacophoric elements is characterized by an almost parallel orientation of a carbonyl and a protonated NH function in conjunction with at least one aromatic ring. Ketocyclazocine is only able to adopt this parallel orientation when the nitrogen is inverted relative to the x-ray structure. Furthermore, two binding sites for the aromatic rings are discussed. The pharmacol. results of all considered bicyclononanone derivs. as well as of the four enantiomers of EMD-61753 can be understood and consistently explained in this way.

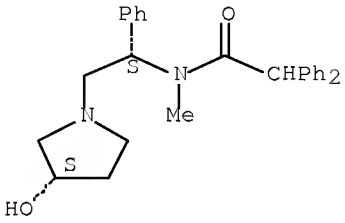
IT 153205-46-0, EMD-61753

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacophore in κ-agonistic diazabicyclo[3.3.1]nonan-9-one-1,5-diesters and arylacetamides)

RN 153205-46-0 CAPLUS

CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 21 THERE ARE 21 CAPLUS RECORDS THAT CITE THIS RECORD (21 CITINGS)

L50 ANSWER 83 OF 87 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1996:51690 CAPLUS Full-text

DOCUMENT NUMBER: 124:193280

ORIGINAL REFERENCE NO.: 124:35427a,35430a

TITLE: The peripherally acting κ-opiate agonist EMD 61753 and Analogs: opioid activity versus peripheral selectivity

AUTHOR(S): Gottschlich, R.; Barber, A.; Bartoszyk, G. D.; Seyfried, C. A.

CORPORATE SOURCE: Preclinical Pharmaceutical Research, E. Merck, Darmstadt, D-64271, Germany

SOURCE: Drugs under Experimental and Clinical Research (1995), 21(5), 171-4
CODEN: DECRDP; ISSN: 0378-6501

PUBLISHER: Bioscience Ediprint

DOCUMENT TYPE: Journal

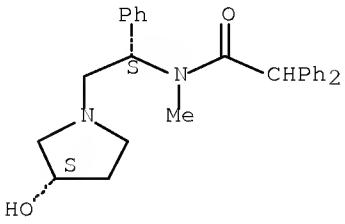
LANGUAGE: English

AB EMD 61753 (N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)-ethyl]2,2-diphenylacetamide hydrochloride) is a peripherally selective κ-opiate agonist. It exhibits antihyperalgesic activity in animal models of inflammatory pain at doses which do not cause signs of central action. The structure of this compound was varied in different ways and the resulting derivs. were tested for affinity to the κ-receptor. Furthermore, those compds. with binding values comparable to that of EMD 61753 were tested for central activity. This was done by measuring the extent to which the haloperidol-induced L-DOPA accumulation in the nucleus accumbens of the rat could be reversed after application of 10 mg/kg s.c. of the test compound Structure-activity relationships revealed that none of the analogs or reference compds. tested is superior to the parent compound with regard to its favorable ratio between κ-receptor affinity and peripheral selectivity.

IT 153205-46-0D, EMD 61753, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(κ-opiate agonist EMD 61753 and analogs structure-related opioid

activity vs. peripheral selectivity)
RN 153205-46-0 CAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (CA INDEX NAME)

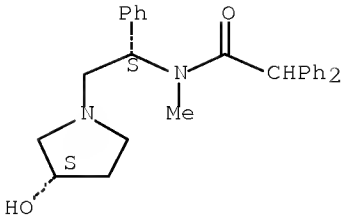
Absolute stereochemistry.



OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

L50 ANSWER 84 OF 87 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1995:293027 CAPLUS Full-text
DOCUMENT NUMBER: 122:177671
ORIGINAL REFERENCE NO.: 122:32297a
TITLE: K-opioid activity of the four stereoisomers of the peripherally selective κ-agonists, EMD 60 400 and EMD 61 753
AUTHOR(S): Gottschlich, Rudolf; Krug, Michael; Barber, Andrew; Devant, Ralf M.
CORPORATE SOURCE: Dep. Medicinal Chem. Biological Res., E. Merck, Darmstadt, Germany
SOURCE: Chirality (1994), 6(8), 685-9
CODEN: CHRLEP; ISSN: 0899-0042
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The four stereoisomers of the two peripherally selective κ-opioid agonists EMD 60 400 and EMD 61 753 were examined for affinity to the κ opioid receptor. The relationships between the configuration of these mols. and their biol. activity are discussed.
IT 153205-46-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(κ-opioid activity of stereoisomers of peripherally selective κ-agonists, EMD 60 400 and EMD 61 753)
RN 153205-46-0 CAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)

L50 ANSWER 85 OF 87 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1995:252056 CAPLUS Full-text
DOCUMENT NUMBER: 122:46289
ORIGINAL REFERENCE NO.: 122:8685a,8688a
TITLE: A pharmacological profile of the novel, peripherally-selective κ-opioid receptor agonist, EMD 61753
AUTHOR(S): Barber, A.; Bartoszyk, G. D.; Bender, H. M.; Gottschlich, R.; Greiner, H. G.; Harting, J.; Mauler, F.; Minck, K.-O.; Murray, R. D.; et al.
CORPORATE SOURCE: Preclinical Pharmaceutical Res., E. Merck, Darmstadt, 64271, Germany
SOURCE: British Journal of Pharmacology (1994), 113(4), 1317-27
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The pharmacol. properties of the novel diarylacetamide κ-opioid receptor agonist, EMD 61753, have been compared with those of ICI 197067 (a centrally-acting κ agonist) and ICI 204448 (a peripherally-selective κ agonist). EMD 61753 binds with high affinity (IC50 5.6 nM) and selectivity (κ:μ:δ:σ binding ratio 1:536:125:>1,786) to κ-opioid receptors and is a full and potent (IC50 54.5 nM) agonist in an in vitro assay for κ-opioid receptors (rabbit vas deferens preparation). Systemically-applied [14C]-EMD 61753 is found in high concns. in the lungs, liver, adrenal glands and kidneys. Considerably less radioactivity is detected in the whole brain, and this radioactivity is concentrated in the region of the cerebral ventricles in the choroid plexuses. EMD 61753 penetrates only poorly into the CNS. EMD 61753 was weakly effective in pharmacol. tests of central activity. This compound reversed haloperidol-induced DOPA accumulation in the nucleus accumbens of the rat only at a dose of 30 mg kg-1, s.c., (doses of 0.1, 1.0 and 10 mg kg-1, s.c., and 1.0, 10 and 100 mg kg-1, p.o., were inactive). Hexobarbitone-induced sleeping in mice was prolonged by EMD 61753 at threshold doses of 10 mg kg-1, s.c., and 100 mg kg-1, p.o., whereas the motor performance of rats in the rotorod test was impaired by EMD 61753 with an ID50 value of 453 mg kg-1, s.c. EMD 61753 produced dose-dependent, naloxone-reversible, antinociception in the mouse formalin test (1st phase ID50 1.9 mg kg-1, s.c., and 10.4 mg kg-1, p.o.: 2nd phase ID50 0.26 mg kg-1, s.c., and 3.5 mg kg-1, p.o.) and rodent abdominal constriction test (ID50 mouse 1.75 mg kg-1, s.c., and 8.4 mg kg-1, p.o.; ID50 rat 3.2 mg kg-1, s.c., and 250 mg kg-1, p.o.). EMD 61753 was inactive, or only weakly effective, in the rat pressure test under normalgesic conditions. After the induction of hyperalgesia with carrageenin, however, this compound elicited potent, dose-dependent (ID50 0.08 mg kg-1, p.o., after prophylactic application) and naloxone-reversible antinociception. The antinociceptive

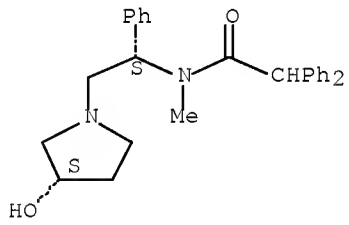
action of systemically-applied (50 mg kg-1, p.o.) EMD 61753 in the hyperalgesic pressure test was completely inhibited by injection of the κ-opioid antagonist nor-binaltorphimine (100 μg) into the inflamed tissue, a result which indicates that this opioid effect is mediated peripherally. Cutaneous plasma protein extravasation produced by antidromic elec. stimulation of the rat saphenous nerve was dose-dependently inhibited by systemically-applied EMD 61753 (ID50 values 3.7 mg kg-1, s.c., and 35.8 mg kg-1, p.o.), and this effect was completely antagonized by intraplanar application of norbinaltorphimine (50 μg). Extravasation elicited by the intraplanar application of substance P (10 μg) was not influenced by the administration of EMD 61753. EMD 61753 produced dose-dependent diuresis in non-hydrated rats at doses of and above 1.0 mg kg-1, s.c., and 10 mg kg-1, p.o., and in saline-loaded rats at doses of and above 10 mg kg-1, s.c., and 30 mg kg-1, p.o. The prostaglandin-mediated fall in mean arterial blood pressure elicited in anesthetized rats by i.v. application of arachidonic acid was not inhibited by prior treatment with EMD 61753 (10 mg kg-1, p.o.). Thus, a blockade of prostaglandin synthesis via inhibition of cyclo-oxygenase activity does not contribute to the in vivo effects of EMD 61753 and its metabolites. The present expts. therefore indicate that EMD 61753 is a potent, selective and orally-effective full κ-opioid receptor agonist which has a limited ability to penetrate the blood-brain barrier and elicit centrally-mediated sedation, putative aversion, diuresis, and antinociception. The inhibitory actions of systemically-applied EMD 61753 against hyperalgesic pressure nociception and neurogenic inflammation are mediated peripherally, probably by opioid receptors on the endings of sensory nerve fibers.

IT 153205-46-0, EMD 61753
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. profile of novel, peripherally-selective κ-opioid receptor agonist, EMD 61753)

RN 153205-46-0 CAPLUS

CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (CA INDEX NAME)

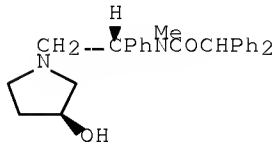
Absolute stereochemistry.



OS.CITING REF COUNT: 59 THERE ARE 59 CAPLUS RECORDS THAT CITE THIS RECORD (59 CITINGS)

L50 ANSWER 86 OF 87 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1994:473054 CAPLUS Full-text
DOCUMENT NUMBER: 121:73054
ORIGINAL REFERENCE NO.: 121:12823a,12826a
TITLE: EMD 61753 as a favorable representative of structurally novel arylacetamido-type κ opiate receptor agonists
AUTHOR(S): Gottschlich, R.; Ackermann, K. A.; Barber, A.; Bartoszyk, G. D.; Greiner, H. E.

CORPORATE SOURCE: Med. Chem. Dep., E. Merck, Darmstadt, D-64271, Germany
SOURCE: Bioorganic & Medicinal Chemistry Letters (1994), 4(5), 677-82
CODEN: BMCLE8; ISSN: 0960-894X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



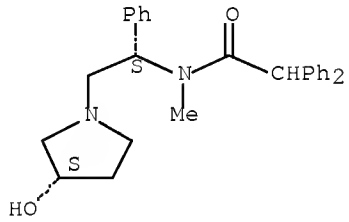
I

AB κ Opiate agonists like (-)-U50488H, (-)-PD 117302, etc., contain an acetamido group which is monosubstituted in the α-position by an aromatic moiety. In contrast, EMD 61753 (I) is disubstituted in this position by two Ph rings and is thus the first representative of the new class of diarylacetamide-type κ opiates. Derivs. of EMD 61753 are described and structure-activity relationships are discussed. In the formalin test in mice EMD 61753 shows a profile similar to that of the anti-inflammatory drugs rather than that of the centrally acting opiates.

IT 153205-46-0P, EMD 61753
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and κ-opiate agonist activity of)

RN 153205-46-0 CAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)

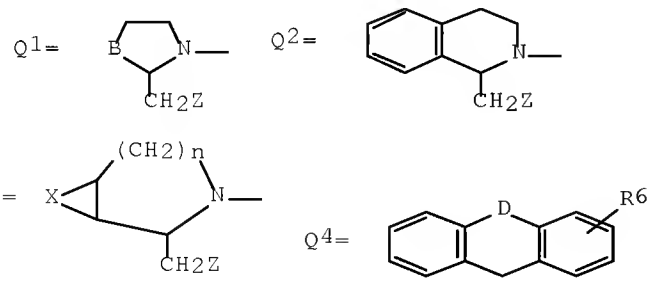
L50 ANSWER 87 OF 87 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1994:163969 CAPLUS Full-text
DOCUMENT NUMBER: 120:163969
ORIGINAL REFERENCE NO.: 120:28923a,28926a
TITLE: Preparation of (pyrrolidinoalkyl)arylacetamides as analgesics and neuroprotectants with high affinity for κ-ligands.
INVENTOR(S): Gottschlich, Rudolf; Ackermann, Karl August; Pruecher, Helmut; Seyfried, Christoph; Greiner, Hartmut; Bartoszyk, Gerd; Mauler, Frank; Stohrer, Manfred;

Barber, Andrew
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: Ger. Offen., 14 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4215213	A1	19931111	DE 1992-4215213	19920509
EP 569802	A1	19931118	EP 1993-107103	19930501
EP 569802	B1	19980715		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
AT 168368	T	19980815	AT 1993-107103	19930501
ES 2121030	T3	19981116	ES 1993-107103	19930501
AU 9338341	A	19931111	AU 1993-38341	19930503
AU 662051	B2	19950817		
CZ 289961	B6	20020515	CZ 1993-823	19930505
RU 2125041	C1	19990120	RU 1993-4806	19930506
CA 2095797	A1	19931110	CA 1993-2095797	19930507
CA 2095797	C	20070918		
NO 9301681	A	19931110	NO 1993-1681	19930507
NO 179789	B	19960909		
NO 179789	C	19961218		
ZA 9303222	A	19931208	ZA 1993-3222	19930507
HU 70172	A2	19950928	HU 1993-1325	19930507
HU 214578	B	19980428		
PL 173779	B1	19980430	PL 1993-298845	19930507
CN 1079219	A	19931208	CN 1993-105673	19930508
CN 1041087	C	19981209		
JP 06049022	A	19940222	JP 1993-108444	19930510
JP 3210771	B2	20010917		
SK 282646	B6	20021008	SK 1993-468	19930512
US 5532266	A	19960702	US 1995-453811	19950530

PRIORITY APPLN. INFO.: DE 1992-4215213 A 19920509
US 1993-57801 B1 19930507

OTHER SOURCE(S): MARPAT 120:163969
GI



AB QCOCR1R2R3 [Q = R4CH(CH2Z)NA, Q1-Q3; R1 = aryl, cycloalkyl, cycloalkylalkyl; R2 = aryl; or R1R2 = Q4; R3 = H, OH, alkoxy, alkyl; R4 = alkyl, (substituted) Ph; R5, R6 = H, F, Cl, Br, iodo, OH, alkoxy, CF3, amino, ureido, NO2, methylenedioxy, etc; B = CH2, O, imino, bond; X = (substituted) condensed ring

system; D = CH2, O, S, imino, CH2CH2, CH:CH, CH2O, bond, etc.; Z = (substituted) 1-pyrrolidinyl; n = 1, 2], were prepared as analgesics and neuroprotectants with a high affinity for κ-receptors (no data). Thus, diphenylacetyl chloride and (1S)-[1-N-methylamino-1-phenyl-2-[(3S)-3-hydroxypyrrolidino]]ethane were stirred in THF to give N-Me N-[(1S)-1-phenyl-2-[(3S)-3- hydroxypyrrolidino]ethyl]-2-diphenylacetamide. Dosage formulations were prepared containing several specific compds. of the invention.

IT 153205-46-0P

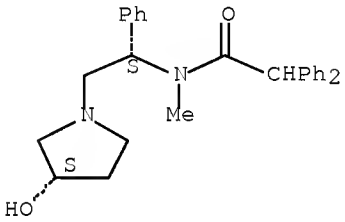
RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of, as analgesic and neuroprotectant with high κ-receptor affinity)

RN 153205-46-0 CAPLUS

CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)

STRUCTURE SEARCH PART 4

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DICTIONARY FILE UPDATES:  28 JUL 2009  HIGHEST RN 1169929-67-2

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L43          14 SEA FILE=REGISTRY SPE=ON  ABB=ON  67198-13-4 OR  67198-13-4/CRN



=> d que l52
L52           1 SEA FILE=REGISTRY SPE=ON  ABB=ON  153205-46-0


=> fil capl; d que l53
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FILE COVERS 1907 - 30 Jul 2009  VOL 151 ISS 5
FILE LAST UPDATED: 29 Jul 2009  (20090729/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Jun 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Jun 2009

CAplus now includes complete International Patent Classification (IPC)
```

reclassification data for the second quarter of 2009.

CAS Information Use Policies apply and are available at:

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This file contains CAS Registry Numbers for easy and accurate substance identification.

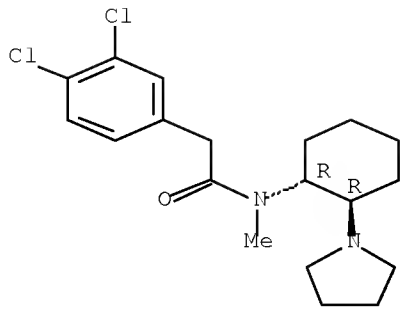
The ALL, BIB, MAX, and STD display formats in the CA/CAplus family of databases have been updated to include new citing references information. This enhancement may impact record import into database management software. For additional information, refer to NEWS 22.
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

L51 1 SEA FILE=REGISTRY SPE=ON ABB=ON 67198-13-4
L53 539 SEA FILE=CAPLUS SPE=ON ABB=ON L51

=> d ibib abs hitstr l53 530-539 10 OLDEST REFERENCES TO EXACT COMPOUND PROVIDED

L53 ANSWER 530 OF 539 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1984:581 CAPLUS Full-text
DOCUMENT NUMBER: 100:581
ORIGINAL REFERENCE NO.: 100:99a,102a
TITLE: The action of κ-agonists on the nociceptive responses of neurons in the medullary dorsal horn of the anesthetized rat
AUTHOR(S): Calthrop, J.; Hill, R. G.
CORPORATE SOURCE: Med. Sch., Univ. Bristol, Bristol, BS8 1TD, UK
SOURCE: Life Sciences (1983), 33(Suppl. 1), 541-4
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Responses of medullary dorsal horn neurons to both mech. and thermal noxious stimuli were recorded in urethane-anesthetized rats. Opiates with reported activity at κ-receptors (tifluadom [83386-35-0], BL 5572M [69815-39-0], and U50488 [67198-13-4]) reduced responses to both noxious stimuli, and in this respect, were indistinguishable from the μ-agonist fentanyl citrate [990-73-8]. These observations are in contrast to the behavioral antinociceptive effects of κ agonists as these substances are active in tests using mech. noxious stimuli, whereas they have little effect in tests with thermal stimuli. It is therefore possible that the modality decoding seen in behavioral expts. occurs at a supraspinal level.
IT 67198-13-4
RL: BIOL (Biological study)
(nociceptive response of spinal cord neuron in relation to)
RN 67198-13-4 CAPLUS
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel- (CA INDEX NAME)

Relative stereochemistry.



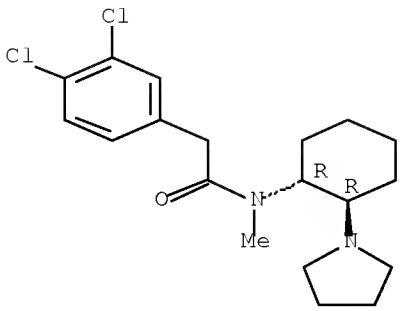
L53 ANSWER 531 OF 539 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1984:569 CAPLUS Full-text
DOCUMENT NUMBER: 100:569
ORIGINAL REFERENCE NO.: 100:95a,98a
TITLE: Opiate receptors in the rat vas deferens
AUTHOR(S): Smith, Colin F. C.; Rance, Michael J.
CORPORATE SOURCE: Reckitt and Colman Pharm. Div., Hull, HU8 7DS, UK
SOURCE: Life Sciences (1983), 33(Suppl. 1), 327-30
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The nature of the opiate receptor population in the rat vas deferens (RVD) was examined by evaluating the interaction of a range of antagonists with prototypic μ-, κ- and α-opioid agonists in the tissue. Ke Values for 5 antagonists against normorphine [466-97-7] in the isolated mouse vas deferens showed excellent correlation with Ke values obtained against the μ-agonist RX783030 [72080-55-8] in the RVD. RX783030 could be effectively antagonized by naltrexone [16590-41-3] in the RVD but not by the α-antagonist ICI 154129 [83420-94-4] whereas D-Ala2,D-Leu5-enkephalin [63631-40-3] required both antagonists to yield parallel shifts of its dose response. The lack of agonist activity of morphine [57-27-2] is a result of the low intrinsic activity of this agent in the RVD. The κ-agonists ethylketocyclazocine [36292-66-7], tifluadom [83386-35-0] and U50488 [67198-13-4] also showed antagonist properties in the RVD. These results can be rationalized by postulating that the RVD contains a μ-receptor population with a high intrinsic activity requirement together with some d-receptors. It is not necessary to propose the existence of a novel ε-receptor in order to rationalize the data reported.

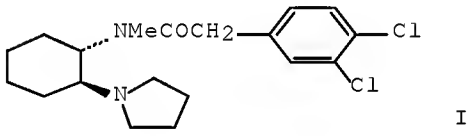
IT 67198-13-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(opiate receptors of vas deferens response to)

RN 67198-13-4 CAPLUS
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel- (CA INDEX NAME)

Relative stereochemistry.



L53 ANSWER 532 OF 539 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1983:119517 CAPLUS Full-text
DOCUMENT NUMBER: 98:119517
ORIGINAL REFERENCE NO.: 98:18061a,18064a
TITLE: U-50,488: a selective and structurally novel non-mu (kappa) opioid agonist
AUTHOR(S): Vonvoigtlander, P. F.; Lahti, R. A.; Ludens, J. H.
CORPORATE SOURCE: Upjohn Co., Kalamazoo, MI, 49001, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1983), 224(1), 7-12
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

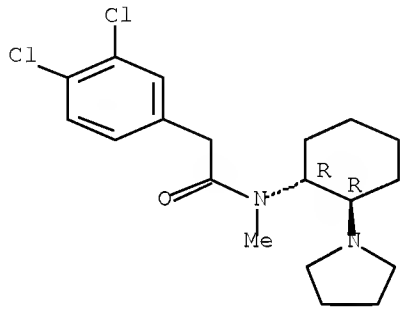


I

AB U-50,488 (I) [67198-13-4] displays analgesic actions in a variety (thermal, pressure and irritant) of assays in mice and rats. Naloxone and MR-2266 block this analgesic effect; thus it is mediated by opioid receptors. However, when compared to morphine analgesia, the naloxone and MR-2266 pA2 values for U-50,488 analgesia were much lower and higher, resp. Likewise, although tolerance occurs to both morphine and U-50,488 analgesia, there was no cross-tolerance between these drugs, and U-50,488 does not cause morphine-type phys. dependence. Apparently, different opioid receptors mediate the analgesic effects of morphine and U-50,488. The effects of U-50,488 appear to be mediated by the so-called κ opioid receptor. In contrast to U-50,488, other reputed κ opioid agonists displayed varying degrees of μ agonist (ketazocine and ethylketocyclazocine) and narcotic antagonist (bremazocine) activities. Thus, U-50,488 is a more selective κ agonist. This conclusion is further supported by binding studies; of all compds. tested, U-50,488 displacement of [3H]ethyllketocyclazocine binding was uniquely not blocked by high concns. of dihydromorphine. In addition to analgesia, this selective κ agonist also causes opioid receptor-mediated sedation, diuresis and corticosteroid elevations. U-50,488 is a useful tool for studying contrasting κ and μ opioid receptor-mediated effects.

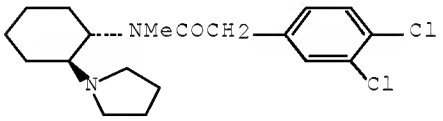
IT 67198-13-4
RL: BIOL (Biological study)
(as κ-opioid agonist)
RN 67198-13-4 CAPLUS
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel- (CA INDEX NAME)

Relative stereochemistry.



OS.CITING REF COUNT: 121 THERE ARE 121 CAPLUS RECORDS THAT CITE THIS RECORD (121 CITINGS)

L53 ANSWER 533 OF 539 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1983:101112 CAPLUS Full-text
DOCUMENT NUMBER: 98:101112
ORIGINAL REFERENCE NO.: 98:15277a,15280a
TITLE: U-50,488, a selective kappa opioid agonist: comparison to other reputed kappa agonists
AUTHOR(S): Von Voigtlander, Philip F.; Lewis, Richard A.
CORPORATE SOURCE: Upjohn Co., Kalamazoo, MI, 49001, USA
SOURCE: Progress in Neuro-Psychopharmacology & Biological Psychiatry (1982), 6(4-6), 467-70
CODEN: PNPPD7; ISSN: 0278-5846
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB U-50488 [trans-3,4-Dichloro-N-methyl-N-(2-(1-pyrrolidinyl)cyclohexyl)benzeneacetamide](I) [67198-13-4] a structurally novel, non-mu opioid, was compared to the reputed kappa opioid agonists, ketazocine, ethylketocyclazocine and bremazocine with respect to analgesic cross tolerance to morphine and U-50488; antagonism of analgesia by naloxone and MR-2266 (in vivo pA2 determination); and narcotic antagonist properties (antagonism of morphine analgesia and precipitation of abstinence in morphine-dependent mice). The analgesic mechanism of bremazocine was similar to that of U-50488 but the former compound had, in addition, considerable mu-antagonist activity. The analgesic mechanisms of the ketazocines were less

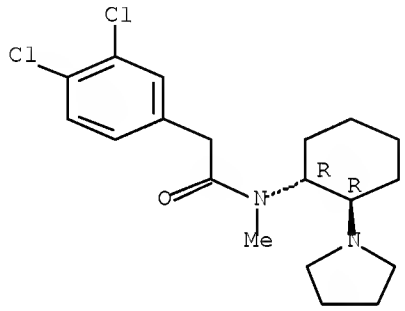
selective; both shared both mu and kappa agonist properties. U-50488, however, had no such mu agonist or antagonist effects and thus is a more selective kappa agonist. Thus, U-50488 and its congeners may prove useful in the elucidation of the functions of kappa receptors in the central nervous system.

IT 67198-13-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(kappa opioid agonist activity of)

RN 67198-13-4 CAPLUS

CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel- (CA INDEX NAME)

Relative stereochemistry.

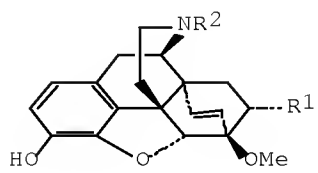


OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)

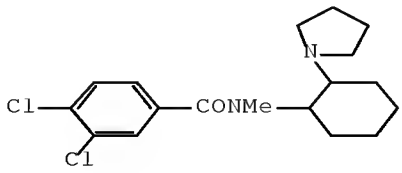
L53 ANSWER 534 OF 539 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER:	1983:100755 CAPLUS Full-text
DOCUMENT NUMBER:	98:100755
ORIGINAL REFERENCE NO.:	98:15192h,15193a
TITLE:	Compounds of novel structure having kappa-agonist behavioral effects in rhesus monkeys
AUTHOR(S):	Katz, Jonathan L.; Woods, James H.; Winger, Gail D.; Jacobson, Arthur E.
CORPORATE SOURCE:	Dep. Pharmacol., Univ. Michigan, Ann Arbor, MI, 48109, USA
SOURCE:	Life Sciences (1982), 31(20-21), 2375-8 CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE:	Journal
LANGUAGE:	English

GI



I



II

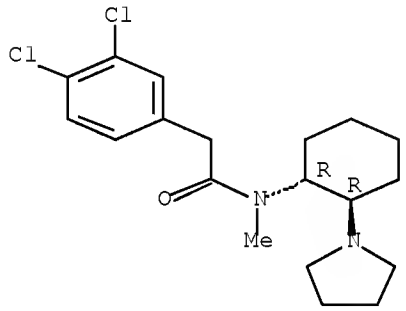
AB The bridged oripavines I, where R1 = COH(Me)(CH2)2CH3 and R2 = cyclopropylmethyl (UM 928 [16527-99-4]) or allyl (UM 736 [23758-80-7]) and R1 = COH(Me)(CH2)2CHMe2 with R2 = cyclopropylmethyl (UM 715 [16614-46-3]), the 2 benzomorphans UM 1246 [71884-78-1] and UM 1250 [84774-03-8], and a compound with a structure not resembling any known narcotic, U 50,488 (II) [67198-13-4], all produced ethylketazocine-like discriminative effects in rhesus monkeys. The N-Me analogs (UM 495 [14521-96-1] and UM 499 [14186-98-2]) of the bridged oripavines tested did not produce ethylketazocine-like discriminative effects, but were quite potent in reversing withdrawal symptoms in morphine-dependent monkeys. With the exception of UM 1250, compds. that produced ethylketazocine-like discriminative effects did not suppress withdrawal symptoms, but rather produced a sedative effect.

IT 67198-13-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(κ-agonistic activity of)

RN 67198-13-4 CAPLUS

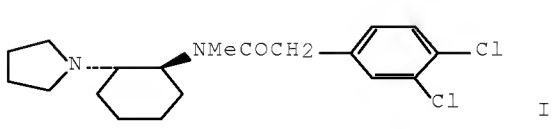
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel- (CA INDEX NAME)

Relative stereochemistry.



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

L53 ANSWER 535 OF 539 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1982:574902 CAPLUS Full-text
DOCUMENT NUMBER: 97:174902
ORIGINAL REFERENCE NO.: 97:29031a,29034a
TITLE: U-50488H, a pure kappa receptor agonist with spinal analgesic loci in the mouse
AUTHOR(S): Piercey, M. F.; Lahti, R. A.; Schroeder, L. A.; Einspahr, F. J.; Barsuhn, C.
CORPORATE SOURCE: Upjohn Co., Kalamazoo, MI, 49001, USA
SOURCE: Life Sciences (1982), 31(12-13), 1197-200
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

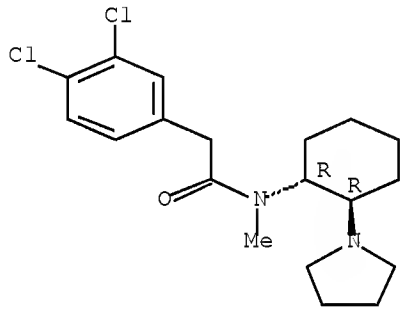
AB U-50488H (I) is a chemical novel analgesic that is a potent opioid-like agent on the mouse tail flick and elec. stimulated guinea pig ileum tests. U-50488H is a very weak competitor for naloxone binding sites in brain and ileum. However, the drug has high affinity for κ receptor binding sites revealed by competition for ethylketocyclazocine sites in the presence of dihydromorphine. Morphine has both supraspinal and spinal sites of action since it was a potent analgesic after both intracranial and intraspinal injections. However, U-50488H works predominantly at the spinal level. Dynorphin may be an endogenous ligand at this site. Studies on cat dorsal horn neurons suggest that U-50488H analgesia may be due to an increase in threshold for neuron excitation.

IT 67198-13-4
RL: BIOL (Biological study)
(analgesia from and κ-agonist activity of, spinal site in relation to)

RN 67198-13-4 CAPLUS

CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel- (CA INDEX NAME)

Relative stereochemistry.



OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)

L53 ANSWER 536 OF 539 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1982:520118 CAPLUS Full-text

DOCUMENT NUMBER: 97:120118

ORIGINAL REFERENCE NO.: 97:19781a,19784a

TITLE: Benzeneacetamide amines: structurally novel non-mμ opioids

AUTHOR(S): Szmuszkovicz, Jacob; Von Voigtlander, Philip F.

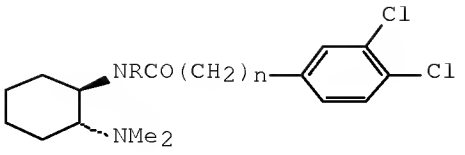
CORPORATE SOURCE: Res. Lab., Upjohn Co., Kalamazoo, MI, 49001, USA

SOURCE: Journal of Medicinal Chemistry (1982), 25(10), 1125-6
CODEN: JMCMAR; ISSN: 0022-2623

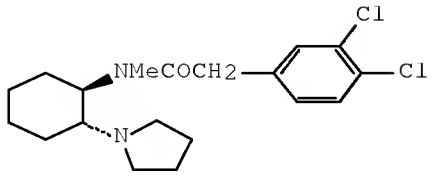
DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I, R=H, n=0
II, R=Me, n=0
III, R=Me, n=1



IV

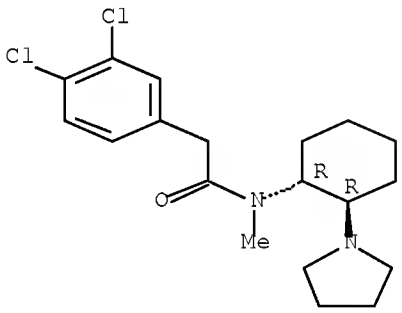
AB Two benzamide amines I [67579-13-9] and II [82657-23-6] and two benzeneacetamide amines III [67197-92-6] and IV [67198-13-4] were synthesized and tested for opioid receptor-mediated pharmacol. activity. I and II had morphine-like behavioral and analgesic activity. In contrast, IV and, to a lesser extent, III had opioid receptor-mediated (naloxone-blocked) analgesic activity, but no behavioral activity. Apparently, the observed activity of IV is due to its non-μ (κ) opioid receptor agonist activity. Structure-activity relations are discussed.

IT 67198-13-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and non-μ opioid receptor-mediated pharmacol. of, structure in relation to)

RN 67198-13-4 CAPLUS

CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel- (CA INDEX NAME)

Relative stereochemistry.



OS.CITING REF COUNT: 52 THERE ARE 52 CAPLUS RECORDS THAT CITE THIS RECORD (52 CITINGS)

L53 ANSWER 537 OF 539 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1982:504137 CAPLUS Full-text
DOCUMENT NUMBER: 97:104137
ORIGINAL REFERENCE NO.: 97:17183a,17186a
TITLE: Opiate effects on plasma corticosteroids: relationship to dysphoria and self-administration
AUTHOR(S): Lahti, R. A.; Collins, R. J.
CORPORATE SOURCE: CNS Dis. Res., Upjohn Co., Kalamazoo, MI, 49001, USA
SOURCE: Pharmacology, Biochemistry and Behavior (1982), 17(1),

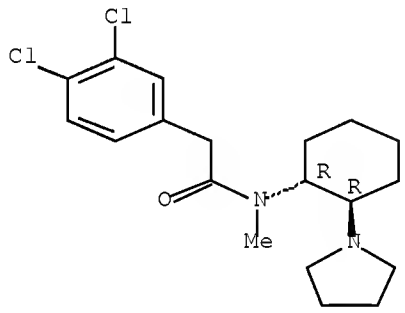
107-9
CODEN: PBBHAU; ISSN: 0091-3057
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Narcotic analgesics administered i.p. to rats raised the concentration of plasma corticosteroids. This effect appears to be a response of the rat to the dysphoric properties of the drug. nalorphine [62-67-9] Or cyclazocine [3572-80-3] which caused dysphoria in man elevate plasma corticosteroids in the rat at relatively low doses. Drugs like morphine [57-27-2] or pentazocine [359-83-1] which induced little dysphoria in man elevate plasma corticosteroids in the rat only at much larger doses. The corticosteroid-elevating effect is mediated by an opiate receptor since naloxone antagonizes the effect of morphine or the analgesic, U-50, 488 [67198-13-4]. Those narcotic analgesics which increased corticosteroid levels at low doses were also found to be poorly self-administered at high rates, elevated corticosteroids only after large doses. The relationship between the dose of a drug which causes elevations in corticosteroid levels and whether or not the drug is self-administered further supports the premise that elevated corticosteroid levels induced by analgesics is due to their dysphoric properties.

IT 67198-13-4
RL: BIOL (Biological study)
(corticosteroids of blood plasma response to, dysphoria and self-administration behavior in relation to)

RN 67198-13-4 CAPLUS
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel- (CA INDEX NAME)

Relative stereochemistry.

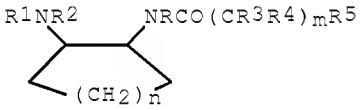


L53 ANSWER 538 OF 539 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1979:439003 CAPLUS Full-text
DOCUMENT NUMBER: 91:39003
ORIGINAL REFERENCE NO.: 91:6357a,6360a
TITLE: N-Acyl-1,2-cyclohexanediamines
INVENTOR(S): Szmuszkovicz, Jacob
PATENT ASSIGNEE(S): Upjohn Co., USA
SOURCE: U.S., 25 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 4145435	A	19790320	US 1976-741354	19761112
CA 1072958	A1	19800304	CA 1977-287468	19770926
ZA 7706241	A	19780726	ZA 1977-6241	19771019
AU 7729881	A	19790426	AU 1977-29881	19771020
AU 510133	B2	19800612		
NL 7711998	A	19780517	NL 1977-11998	19771101
DE 2749950	A1	19780518	DE 1977-2749950	19771108
DE 2749950	C2	19880225		
CH 638777	A5	19831014	CH 1977-13623	19771108
BE 860726	A1	19780510	BE 1977-182548	19771110
JP 53063351	A	19780606	JP 1977-135227	19771110
JP 01014231	B	19890310		
FR 2370723	A1	19780609	FR 1977-33971	19771110
FR 2370723	B1	19800822		
GB 1569225	A	19800611	GB 1977-46746	19771110
JP 61233654	A	19861017	JP 1986-94401	19860423
JP 62059101	B	19871209		
JP 61243053	A	19861029	JP 1986-94399	19860423
JP 62059100	B	19871209		
JP 61243054	A	19861029	JP 1986-94400	19860423
JP 62059103	B	19871209		

PRIORITY APPLN. INFO.: US 1976-741354 A 19761112
OTHER SOURCE(S): MARPAT 91:39003
GI



I

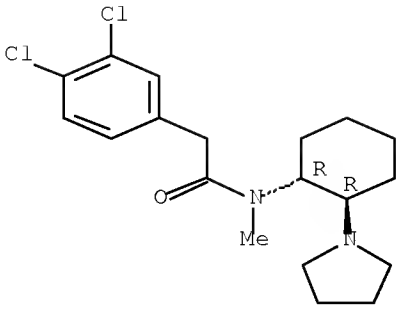
AB Diamines trans-I [n = 2,3,4; R = C1-3 alkyl; R1 and R2 are alkyl, CH2CF3, 2-alken-1-yl, hydroxyalkyl, cycloalkyl, cycloalkylmethyl, phenylalkyl, or NR1R2 = saturated heterocycle; R3 and R4 are H or Me, or R3R4 = CH2CH2; m = 1,2,3,4; R5 = 1- or 2-naphthyl, (trifluoromethyl)-, alkyl-, alkoxy-, azido-, or phenylphenyl], useful as analgesics and antitussives (no data), were prepared by N-acylation. The reaction of trans-N,N,N'-trimethyl-1,2-cyclohexanediamine with 4-BrC6H4CH2CO2H and N,N'-carbonyldiimidazole in THF gave trans-N,N,N'-trimethyl-N'-(4-bromophenylacetyl)-1,2-cyclohexanediamine.

IT 67198-13-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 67198-13-4 CAPLUS

CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel- (CA INDEX NAME)

Relative stereochemistry.

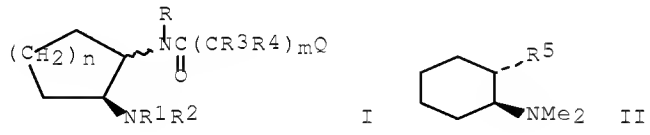


OS.CITING REF COUNT: 29 THERE ARE 29 CAPLUS RECORDS THAT CITE THIS RECORD (29 CITINGS)

L53 ANSWER 539 OF 539 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1978:546631 CAPLUS Full-text
DOCUMENT NUMBER: 89:146631
ORIGINAL REFERENCE NO.: 89:22713a,22716a
TITLE: Arylacylamide derivatives
INVENTOR(S): Szmuszkovicz, Jacob
PATENT ASSIGNEE(S): Upjohn Co., USA
SOURCE: Ger. Offen., 105 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2749950	A1	19780518	DE 1977-2749950	19771108
DE 2749950	C2	19880225		
US 4145435	A	19790320	US 1976-741354	19761112
PRIORITY APPLN. INFO.:			US 1976-741354 A	19761112

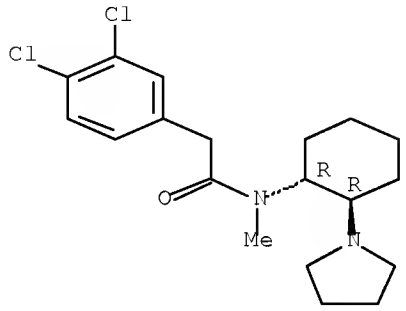
GI



AB Thirty-eight arylacylamides I (R = H, C1-3 alkyl; R1, R2 = H, C1-6 aliphatic, C3-6 cycloalkyl, phenylalkyl; NR1R2 = N1-2 heterocyclyl; R3, R4 = H, Me; CR3R4 = cyclopropyl; m = 1-4; m = 1-8; Q = naphthyl, substituted phenyl) and their pharmaceutically acceptable salts, useful as analgesics, were prepared by 11 methods. Thus, aminolysis of 7-azabicyclo[4.1.0]heptane with aqueous Me2NH gave 46% cyclohexanediamine II (R5 = NH2) which was formylated with HCO2Et to give 85% formamide II (R5 = NHCHO). This was reduced with LiAlH4 to give 82% II (R5 = NHMe) which was acylated carbonyldiimidazole and 4-BrC6H4CH2CO2H and the mixture stirred 18 h to give 78% II (R5 = NMeCOCH2C6H4Br-4), characterized as the HCl salt. Typical I had ED50 <75mg/kg s.c. in standard analgesic tests; the more effective I had ED50 <10 mg/kg s.c. in standard tests while showing ED50 <100 mg/kg s.c. in the naxolone spring test.

IT 67198-13-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 67198-13-4 CAPLUS
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel- (CA INDEX NAME)

Relative stereochemistry.



STRUCTURE SEARCH PART 5

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L43 14 SEA FILE=REGISTRY SPE=ON ABB=ON 67198-13-4 OR 67198-13-4/CRN

L49 1545 SEA FILE=CAPLUS SPE=ON ABB=ON L43

=> s l49 not l53
L57 1006 L49 NOT L53 10 OLDEST REFERENCES TO SALTS

=> d ibib abs hitstr l57 997-1006

L57 ANSWER 997 OF 1006 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1984:96573 CAPLUS Full-text
DOCUMENT NUMBER: 100:96573
ORIGINAL REFERENCE NO.: 100:14529a,14532a
TITLE: In vivo studies on spinal opiate receptor systems mediating antinociception. II. Pharmacological profiles suggesting a differential association of mu, delta and kappa receptors with visceral chemical and cutaneous thermal stimuli in the rat
AUTHOR(S): Schmauss, Claudia; Yaksh, Tony L.
CORPORATE SOURCE: Dep. Neurosurgical Res., Mayo Clin., Rochester, MN, 55905, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1984), 228(1), 1-12
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The intrathecal administration of μ (morphine [57-27-2]) and δ (D-Ala2-D-Leu5-enkephalin [63631-40-3]) but not κ agonists (ethylketocyclazocine [36292-66-7], bremazocine [75684-07-0], and U50488H [83913-06-8]) or partial agonists (nalbuphine [20594-83-6] and buprenorphine [52485-79-7]) produced a dose-dependent inhibition of all cutaneous thermal (hot plate and tail-flick) responses in the rat. In contrast, on visceral chemical tests (writhing), μ and κ agonists but not δ agonists exerted a powerful suppression of the response. Whereas the ED50 of morphine on the cutaneous thermal tests did not differ from that observed on the visceral chemical test, agents with significant μ and δ activity (metkephamid [66960-34-7] and β-endorphin [60617-12-1]) showed a prominent reduction in activity on the writhing as compared with the hot plate and tailflick. Systemic naloxone [465-65-6] resulted in a dose-dependent antagonism of the effect of all intrathecal agents. Estimation of the pA2 of μ agents indicated no difference on the hot plate/tail-flick and writhing (pA2 approx. 7). κ Ligands were selectively resistant to antagonism with naloxone pA2 values for those agonists ranging from 5.9 to 6.6. Apparently, there are 3 discriminable populations of receptors in the spinal cord whose activation results in a selective modulation of the response of the animal to noxious stimuli. In addition, the selective effects of the δ agonists on cutaneous thermal and κ agonists on visceral chemical stimuli suggest a differential coding of spinal afferents through which these stimuli are transmitted.

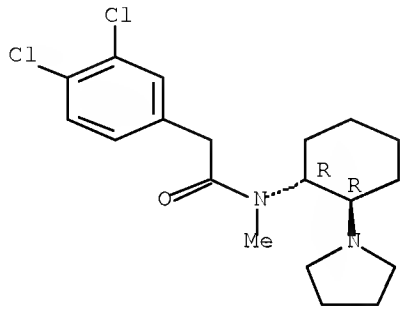
IT 83913-06-8
RL: BIOL (Biological study)
(opiate receptor of spinal cord in antinociception in relation to)

RN 83913-06-8 CAPLUS
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

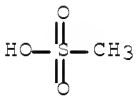
CRN 67198-13-4
CMF C19 H26 Cl2 N2 O

Relative stereochemistry.



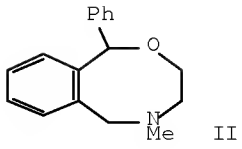
CM 2

CRN 75-75-2
CMF C H4 O3 S



OS.CITING REF COUNT: 61 THERE ARE 61 CAPLUS RECORDS THAT CITE THIS RECORD (61 CITINGS)

L57 ANSWER 998 OF 1006 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1984:96538 CAPLUS Full-text
DOCUMENT NUMBER: 100:96538
ORIGINAL REFERENCE NO.: 100:14521a,14524a
TITLE: Involvement of biogenic amines with the mechanisms of novel analgesics
AUTHOR(S): Vonvoigtlander, Philip F.; Lewis, Richard A.; Neff, Gary L.; Triezenberg, Herman J.
CORPORATE SOURCE: Upjohn Co., Kalamazoo, MI, 49001, USA
SOURCE: Progress in Neuro-Psychopharmacology & Biological Psychiatry (1983), 7(4-6), 651-6
CODEN: PNPPD7; ISSN: 0278-5846
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



II

AB The analgesic activity of the κ-opioid agonist, U-50,488H (I) [83913-06-8] was markedly antagonized by pretreatment with reserpine, p-chlorophenylalanine, and ketanserin. Since analgesic doses of U-50,488H enhance serotonin metabolism, these results suggest that κ-analgesia requires serotonin acting through 5-HT2 receptors. The nonopioid analgesic nefopam (II) [13669-70-0], though a blocker of biogenic amine uptake, displays an analgesic spectrum of action more similar to that of amphetamine than to that of the tricyclic antidepressants or serotonin-uptake blockers. p-Chlorophenylalanine and ketanserin do not block nefopam analgesia, nor do naloxone, atropine, yohimbine, propranolol, or haloperidol. However, as reserpine does block nefopam analgesia, biogenic amines acting at other receptors may be involved. The observation that m-tyrosine [775-06-4] causes behavioral effects similar to high doses of nefopam suggested that they might be acting through similar mechanisms. However, although m-tyrosine causes analgesia, it is blocked by yohimbine. This suggests that alpha2-adrenoreceptors are involved in m-tyrosine analgesia and that it differs in mechanism from nefopam analgesia.

IT 83913-06-8
RL: BIOL (Biological study)
(analgesia from, biogenic amines in relation to)

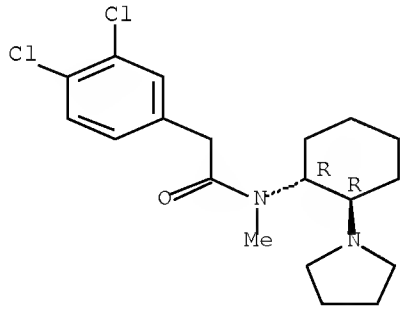
RN 83913-06-8 CAPLUS

CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

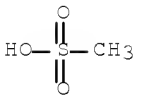
CRN 67198-13-4
CMF C19 H26 Cl2 N2 O

Relative stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

L57 ANSWER 999 OF 1006 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1984:61632 CAPLUS Full-text
DOCUMENT NUMBER: 100:61632
ORIGINAL REFERENCE NO.: 100:9285a,9288a
TITLE: Further study of kappa opioids on increased urination
AUTHOR(S): Leander, J. David
CORPORATE SOURCE: Lilly Res. Lab., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1983), 227(1), 35-41
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

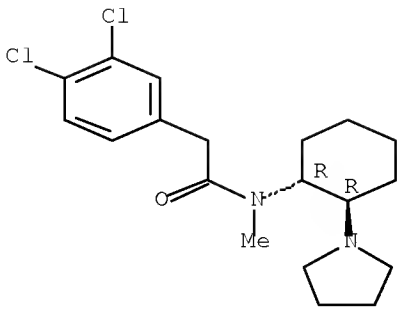
AB The effects of various opioid agonists and antagonists on urination were studied in the normally hydrated rat. Two κ agonists, U-50488H [83913-06-8] and proxorphan tartrate [69815-39-0], markedly increased urination. The increased urination produced by U-50,488H was antagonized by opioid antagonists in a potency order which indicated that the effects were due to an action at κ opioid receptors. μ Agonists decreased urination and were blocked by low doses (0.01 and 0.1 mg/kg) of naloxone [465-65-6], whereas κ agonists increased urination and were only blocked by a high dose (10 mg/kg) of naloxone. The diuretic effects of U-50,488H and ketazocine [36292-69-0], but not proxorphan and bremazocine [75684-07-0], were reduced by morphine [57-27-2], consistent with the idea that proxorphan and bremazocine have morphine antagonist activity. Water derivation produced a shift to the right for the dose-effect curve for bremazocine-induced diuresis. κ Agonists were ineffective in increasing urination in Brattleboro rats that were homozygous for diabetes insipidus, whereas μ agonists were still effective in decreasing urination. Apparently, κ agonists inhibit release of vasopressin [11000-17-2] from the neurohypophysis and this decrease in vasopressin release leads to increased urination. The effects of opioids on urination in the normally hydrated rat can be extremely useful in classifying the activities of opioid on μ and κ receptors in vivo.

IT 83913-06-8
RL: BIOL (Biological study)
(diuresis from, opiate receptor subtypes in relation to)
RN 83913-06-8 CAPLUS
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

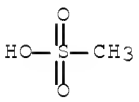
CRN 67198-13-4
CMF C19 H26 Cl2 N2 O

Relative stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)

L57 ANSWER 1000 OF 1006 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1984:17578 CAPLUS Full-text
DOCUMENT NUMBER: 100:17578
ORIGINAL REFERENCE NO.: 100:2675a,2678a
TITLE: Hyperalgesic effect of the selective kappa opioid agonist, U-50488H in mice
AUTHOR(S): Ramabadran, Krishnaswami
CORPORATE SOURCE: Fac. Med., Natl. Univ. Singapore, Singapore, 0511, Singapore
SOURCE: Japanese Journal of Pharmacology (1983), 33(6), 1289-92
CODEN: JJPAAZ; ISSN: 0021-5198
DOCUMENT TYPE: Journal
LANGUAGE: English

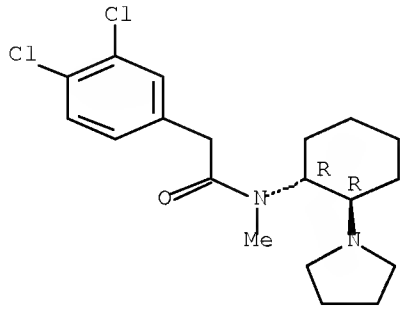
AB Comparative expts. in mice, using the 2 putative κ-agonists U-50488H (I) [83913-06-8] and (-)-bremazocine (II) [75684-07-0], showed that both could produce hyperalgesia in the hot-plate test, but differed in their ability to antagonize morphine-induced antinociception. II completely antagonized the morphine action, whereas I did not, suggesting that II has strong μ-antagonist properties as well as κ-agonist ones. I appears to be a more selective κ-agonist and may be useful as a pharmacol. tool for evaluating and contrasting κ- and μ-opioid receptor-mediated effects.

IT 83913-06-8
RL: PRP (Properties)
(hyperalgesic effect of, κ-opioid receptors in relation to)
RN 83913-06-8 CAPLUS
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

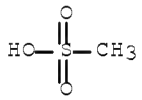
CRN 67198-13-4
CMF C19 H26 Cl2 N2 O

Relative stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



L57 ANSWER 1001 OF 1006 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1984:1004 CAPLUS Full-text
DOCUMENT NUMBER: 100:1004
ORIGINAL REFERENCE NO.: 100:171a,174a
TITLE: Differential association of spinal μ, δ and κ opioid receptors with cutaneous thermal and visceral chemical nociceptive stimuli in the rat
AUTHOR(S): Schmauss, C.; Yaksh, T. L.; Shimohigashi, Y.; Harty, G.; Jensen, T.; Rodbard, D.
CORPORATE SOURCE: Mayo Clin., Rochester, MN, USA
SOURCE: Life Sciences (1983), 33(Suppl. 1), 653-6
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The intrathecal administration of μ- (morphine [57-27-2]), δ- ([D-Ala2,D-Leu5]-enkephalin [63631-40-3], and dimeric leucine-enkephalin [82221-89-4]), and the mixed μ/δ- (β-endorphin [60617-12-1]) agonists dose-dependently inhibited all cutaneous thermal (tail flick/hot plate) nociceptive responses in the rat. The κ-agonist U50488H [83913-06-8] had no analgesic potency in thermal nociceptive tests. In the visceral chemical test (writhing), β-endorphin, morphine, and U50488H exerted a powerful suppression of the response. In contrast at doses 10-50 times the ED50 on cutaneous thermal

tests, the δ-agonist had no effect on the writhing response. At higher intrathecal doses, δ ligands produced flaccidity. The existence of 3 discriminable populations of opioid receptors in the spinal cord whose activation has different effects on the animal's response to noxious stimuli is indicated.

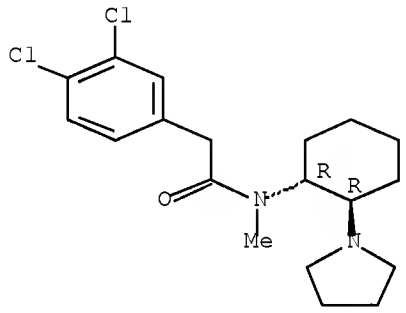
IT 83913-06-8
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(analgesic activity of, in spinal cord, opiate receptor subtypes in relation to)

RN 83913-06-8 CAPLUS
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

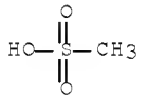
CRN 67198-13-4
CMF C19 H26 Cl2 N2 O

Relative stereochemistry.



CM 2

CRN 75-75-2
CMF C H4 O3 S



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

L57 ANSWER 1002 OF 1006 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1983:588496 CAPLUS Full-text
DOCUMENT NUMBER: 99:188496
ORIGINAL REFERENCE NO.: 99:28866h,28867a
TITLE: Simultaneous differentiation of three opiate receptor subpopulations by computer modeling
AUTHOR(S): Maurer, R.; Engel, G.

CORPORATE SOURCE: Preclin. Res., Sandoz Ltd., Basel, CH-4002, Switz.
SOURCE: Journal of Receptor Research (1983), 3(1-2), 219-25
CODEN: JRERDM; ISSN: 0197-5110
DOCUMENT TYPE: Journal
LANGUAGE: English

AB [3H]-(-)-bremazocine was displaced from guinea pig brain membrane homogenates by 3 compds. having different specificities to opiate receptor subpopulations. A 3-site receptor model showed the best fit of the calculated to the measured value for the μ-receptor specific compound [D-Ala2,MePhe4,Gly(ol)5]-enkephalin [78123-71-4] and the δ-receptor specific compound [D-Ala2,D-Leu5]-enkephalin [63631-40-3]. Computer modeling of data from displacement curves with the κ-receptor specific compound U-50,488H [83913-06-8] favored a 2-site receptor model.

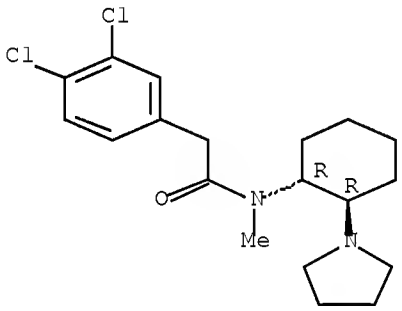
IT 83913-06-8
RL: BIOL (Biological study)
(opiate receptor binding of, in brain, computer modeling in)

RN 83913-06-8 CAPLUS
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 67198-13-4
CMF C19 H26 Cl2 N2 O

Relative stereochemistry.



CM 2

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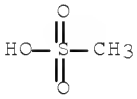
CMF C H4 O3 S



L57 ANSWER 1003 OF 1006 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1983:533543 CAPLUS Full-text
DOCUMENT NUMBER: 99:133543

ORIGINAL REFERENCE NO.: 99:20397a,20400a
TITLE: Multiple opiate receptor affinities of kappa and agonist/antagonist analgesics: in vivo assessment
AUTHOR(S): Wood, Paul L.; Sanschagrin, D.; Richard, J. W.; Thakur, M.
CORPORATE SOURCE: Douglas Hosp. Res. Cent., Verdun, QC, H4H 1R3, Can.
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1983), 226(2), 545-50
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The affinities of κ and agonist/antagonist (Ag/Ant) analgesics for mu and delta opiate receptors were examined in vivo in the rat. In the case of κ agonists, these agents appear to be μ and δ antagonists in vivo. The μ antagonist activity appears to involve a specific isoreceptor population, namely μ-2 receptors. With Ag/Ant analgesics, a more complex pharmacol. is evident such that at μ and δ receptor populations these agents can exhibit pure Ag, pure Ant or a combination of Ag and Ant actions. These activities vary with the neuronal localization of the receptor population being examined In addition, complex species differences are evident with Ag/Ant actions.

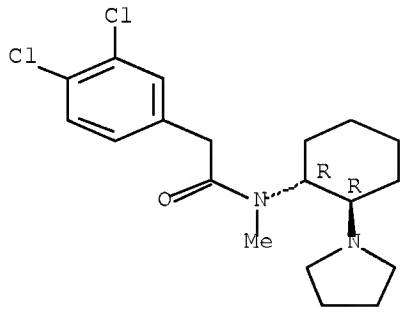
IT 83913-06-8
RL: PRP (Properties)
(multiple opiate receptor affinity of)

RN 83913-06-8 CAPLUS
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 67198-13-4
CMF C19 H26 Cl2 N2 O

Relative stereochemistry.



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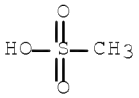


L57 ANSWER 1004 OF 1006 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1983:11355 CAPLUS Full-text
DOCUMENT NUMBER: 98:11355
ORIGINAL REFERENCE NO.: 98:1773a,1776a
TITLE: Properties of a selective kappa agonist, U-50,488H
AUTHOR(S): Lahti, R. A.; VonVoigtlander, P. F.; Barsuhn, C.
CORPORATE SOURCE: Upjohn Co., Kalamazoo, MI, 49001, USA
SOURCE: Life Sciences (1982), 31(20-21), 2257-60
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English

AB U-50488H (I) [83913-06-8] was shown to be a naloxone-antagonizable analgesic in rodents. However, the dose of naloxone needed for antagonism was higher than it was for morphine. I did not produce phys. dependence; however it did produce tolerance upon chronic administration. I was cross tolerant with bremazocine but not with morphine. Monkeys trained to discriminate ethylketocyclazocine (EKC) from saline showed a complete generalization to I but not to morphine. The evaluation of I in 3H-EKC site-selective binding indicated that it has a high affinity for the κ receptor and a low affinity for the μ receptor. I appears to be a selective inhibitor of opioid κ receptors.

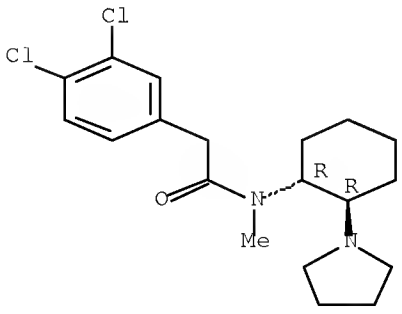
IT 83913-06-8
RL: BIOL (Biological study)
(κ-opioid receptor agonist, pharmacol. of)

RN 83913-06-8 CAPLUS
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[(1R,2R)-2-(1-pyrrolidinyl)cyclohexyl]-, rel-, methanesulfonate (1:1) (CA INDEX NAME)

CM 1

CRN 67198-13-4
CMF C19 H26 Cl2 N2 O

Relative stereochemistry.



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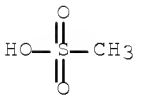
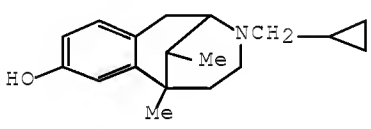
CMF C H4 O3 S



OS.CITING REF COUNT: 42 THERE ARE 42 CAPLUS RECORDS THAT CITE THIS RECORD (42 CITINGS)

L57 ANSWER 1005 OF 1006 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1981:150270 CAPLUS Full-text
DOCUMENT NUMBER: 94:150270
ORIGINAL REFERENCE NO.: 94:24447a,24450a
TITLE: Generalization study with some narcotic and nonnarcotic psychoactive drugs in rats trained to discriminate between cyclazocine and saline
AUTHOR(S): McCarten, Michael D.; Lal, Harbans
CORPORATE SOURCE: Dep. Pharmacol. Toxicol., Univ. Rhode Island, Kingston, RI, 02881, USA
SOURCE: Endog. Exog. Opiate Agonists Antagonists, Proc. Int. Narc. Res. Club Conf. (1980), Meeting Date 1979, 439-42. Editor(s): Way, E. Leong. Pergamon: Elmsford, N. Y.
CODEN: 45EWA5
DOCUMENT TYPE: Conference
LANGUAGE: English
GI

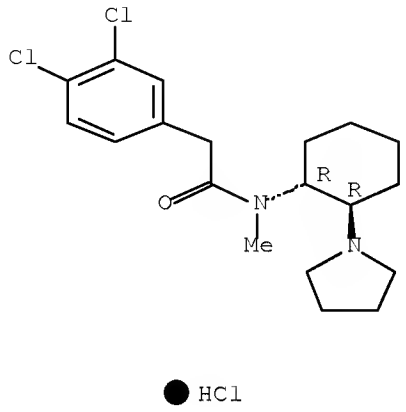


I

AB In an operant behavior procedure of lever pressing on an FR10 schedule of food reinforcement, male rats were trained to respond on a lever on 1 side of the food cup following a cyclazocine (I) [3572-80-3] (1.25 mg/kg) injection and to respond on a lever on the alternate side following a saline injection. The trained rats selected the cyclazocine lever in a dose-dependent manner based entirely upon the interoceptive stimuli produced by cyclazocine. The stimuli generalized completely to ethylketocyclazocine [36292-66-7], morphine [57-27-2] and nalorphine [62-67-9], only partially to pentazocine [359-83-1], and none to aceperone [807-31-8], amphetamine [300-62-9], amitriptyline [50-48-6], apomorphine [58-00-4], benperidol [2062-84-2], dl-butaclamol [51152-91-1], chlorpromazine [50-53-3], clonidine [4205-90-7], clozapine [5786-21-0], desipramine [50-47-5], dexclamol [52340-25-7], haloperidol [52-86-8], oxiperomide [5322-53-2], and pipamperone [1893-33-0].
IT 67197-96-0
RL: BIOL (Biological study)
(behavior response to cyclazocine generalization to)

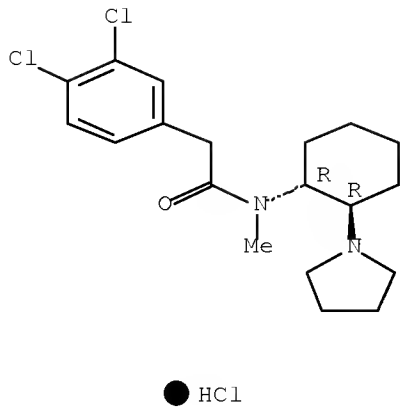
RN 67197-96-0 CAPLUS
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-, monohydrochloride, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L57 ANSWER 1006 OF 1006 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1980:488589 CAPLUS Full-text
DOCUMENT NUMBER: 93:88589
ORIGINAL REFERENCE NO.: 93:14047a,14050a
TITLE: Annual report: dependence studies of new compounds in the rhesus monkey (1979)
AUTHOR(S): Aceto, M. D.; Harris, L. S.; Dewey, W. L.; May, E. L.
CORPORATE SOURCE: Med. Coll. Virginia, Virginia Commonw. Univ., Richmond, VA, 23298, USA
SOURCE: NIDA Research Monograph (1979), 27(Probl. Drug Depend.), 330-50
CODEN: MIDAD4; ISSN: 0361-8595
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tail-flick agonist, morphine antagonist, phenylquinone, hot plate, and Nilsen tests were used to provide a preliminary estimate of the potency and profile of activity for 32 compds. in monkeys. Most of the compds. did not substitute or only partially substituted for morphine. Several, such as loperamide [53179-11-6], 8β-methyldihydrocodeinone-HCl [71968-06-4], and 3,6-dideoxydihydromorphine-HCl [69663-46-3] substituted completely for morphine; the 1st 2 appeared to be as potent as morphine.
IT 67197-96-0
RL: BIOL (Biological study)
(dependence liability of)
RN 67197-96-0 CAPLUS
CN Benzeneacetamide, 3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-, monohydrochloride, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

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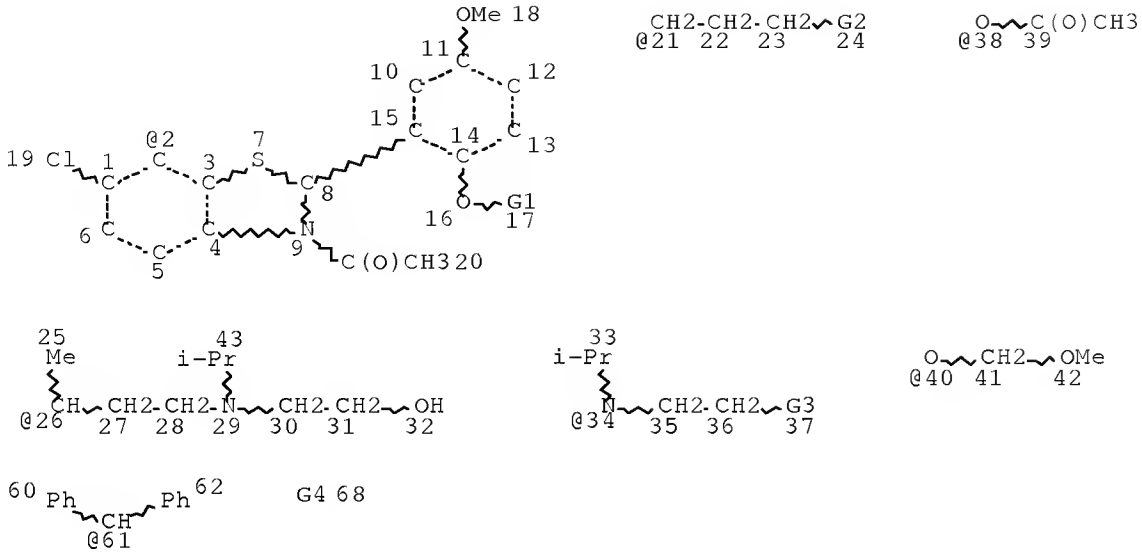
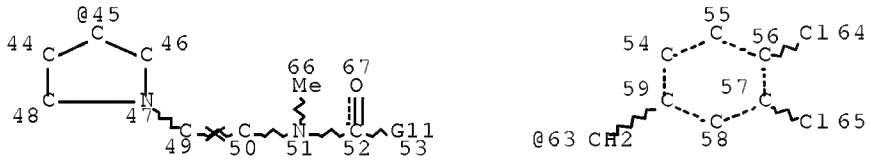


Page 1-A



Page 2-A
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VAR G2=34/CL
VAR G3=38/OET/40/OH/OME
VAR G4=2/45
VAR G11=63/61
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NSPEC IS RC AT 49
NSPEC IS RC AT 50
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 68

STEREO ATTRIBUTES: NONE
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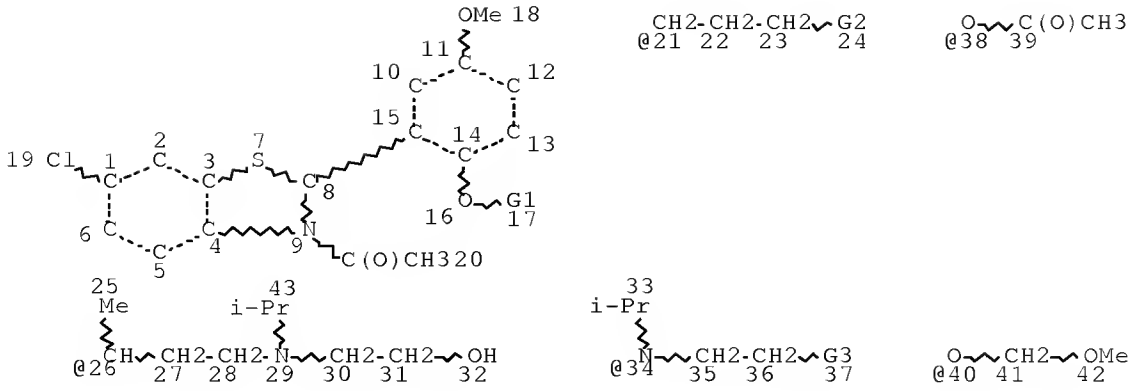
L8 STR



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VAR G2=34/CL
VAR G3=38/OET/40/OH/OME
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 43

STEREO ATTRIBUTES: NONE
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100.0% PROCESSED 33 ITERATIONS 33 ANSWERS
SEARCH TIME: 00.00.01

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FILE 'REGISTRY' ENTERED AT 07:16:29 ON 30 JUL 2009
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L2 STR L1
L3 3 SEA SSS SAM L2
L4 774 SEA SSS FUL L2
SAVE TEMP L4 JEA742FULL/A
ACT JEA742REG/A

L5 11 SEA SPE=ON ABB=ON (185951-07-9/BI OR 610308-87-7/BI OR 610308-92-4/BI OR 610309-27-8/BI OR 610309-63-2/BI OR 823204-37-1/BI OR 823204-39-3/BI OR 823204-44-0/BI OR 823204-46-2/BI OR 823791-11-3/BI OR 83913-06-8/BI)

L6 11 SEA SPE=ON ABB=ON L4 AND L5

FILE 'ZCAPLUS' ENTERED AT 07:29:30 ON 30 JUL 2009
L7 1880 SEA SPE=ON ABB=ON L4

FILE 'REGISTRY' ENTERED AT 07:29:39 ON 30 JUL 2009

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L10          33 SEA SUB=L4 SSS FUL L8
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L11             STR L2
L12           1 SEA SUB=L4 SSS SAM L11
                D SCA
L13             STR L11
L14           0 SEA SUB=L4 SSS SAM L13
L15          63 SEA SUB=L4 SSS FUL L13
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L16          15 SEA SPE=ON  ABB=ON  L15 AND 4/NR
L17          58 SEA SPE=ON  ABB=ON  L15 AND CL/ELS
L18          10 SEA SPE=ON  ABB=ON  L16 AND L17
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                D SCA
L19           7 SEA SPE=ON  ABB=ON  L18 AND A
L20        1631 SEA SPE=ON  ABB=ON  C27H30N2O2
L21           8 SEA SPE=ON  ABB=ON  L18 NOT L20
                SAVE TEMP L21 JEA742SUB3/A
L22           7 SEA SPE=ON  ABB=ON  L16 NOT L21
                D SCA
                SAVE TEMP L22 JEA742SUB4/A
L23          15 SEA SPE=ON  ABB=ON  (L21 OR L22)
L24          48 SEA SPE=ON  ABB=ON  L17 NOT L16
                D SCA
L25       64888 SEA SPE=ON  ABB=ON  OXASPIRO
L26           3 SEA SPE=ON  ABB=ON  L24 AND L25
                D SCA
L27          11 SEA SPE=ON  ABB=ON  (L21 OR L26)
                SAVE TEMP L27 JEA742SUB3/A
L28          45 SEA SPE=ON  ABB=ON  L24 NOT L25
                SAVE TEMP L28 JEA742SUB5/A

     FILE 'CAPLUS' ENTERED AT 07:55:12 ON 30 JUL 2009
                ACT JEA742CAAU/A
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L29           1 SEA SPE=ON  ABB=ON  US2005-562742/AP
               ---------
L30        1366 SEA SPE=ON  ABB=ON  SHIMOMURA K?/AU
L31         387 SEA SPE=ON  ABB=ON  AONO H?/AU
L32         516 SEA SPE=ON  ABB=ON  TSUKAHARA Y?/AU
L33        2370 SEA SPE=ON  ABB=ON  HATA T?/AU
L34        1880 SEA SPE=ON  ABB=ON  L4
L35           3 SEA SPE=ON  ABB=ON  L10
L36         195 SEA SPE=ON  ABB=ON  L27
L37          87 SEA SPE=ON  ABB=ON  L22
L38        1606 SEA SPE=ON  ABB=ON  L28
L39           1 SEA SPE=ON  ABB=ON  (L29 OR L30 OR L31 OR L32 OR L33) AND L34

     FILE 'REGISTRY' ENTERED AT 07:57:48 ON 30 JUL 2009
L40           1 SEA SPE=ON  ABB=ON  L5 AND L27
                D IDE
L41           2 SEA SPE=ON  ABB=ON  823791-10-2 OR  823791-10-2/CRN
L42           1 SEA SPE=ON  ABB=ON  L5 AND L28
                D IDE
L43          14 SEA SPE=ON  ABB=ON  67198-13-4 OR  67198-13-4/CRN
L44           1 SEA SPE=ON  ABB=ON  L22 AND L5
                D IDE
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L45           2 SEA SPE=ON  ABB=ON  153205-46-0 OR 153205-46-0/CRN
L46          14 SEA SPE=ON  ABB=ON  67198-13-4 OR  67198-13-4/CRN
L47           2 SEA SPE=ON  ABB=ON  153205-46-0 OR 153205-46-0/CRN

     FILE 'CAPLUS' ENTERED AT 08:04:05 ON 30 JUL 2009
L48           2 SEA SPE=ON  ABB=ON  L41
L49        1545 SEA SPE=ON  ABB=ON  L43
L50          87 SEA SPE=ON  ABB=ON  L45

     FILE 'REGISTRY' ENTERED AT 08:04:29 ON 30 JUL 2009
L51           1 SEA SPE=ON  ABB=ON  67198-13-4
L52           1 SEA SPE=ON  ABB=ON  153205-46-0

     FILE 'CAPLUS' ENTERED AT 08:04:58 ON 30 JUL 2009
L53         539 SEA SPE=ON  ABB=ON  L51
L54          82 SEA SPE=ON  ABB=ON  L52

     FILE 'CAPLUS' ENTERED AT 08:07:05 ON 30 JUL 2009
                D QUE NOS L39
                D IBIB ABS HITSTR L39

     FILE 'REGISTRY' ENTERED AT 08:07:38 ON 30 JUL 2009
                D STAT QUE L10

     FILE 'CAPLUS' ENTERED AT 08:07:38 ON 30 JUL 2009
                D QUE NOS L35
L55           2 SEA SPE=ON  ABB=ON  L35 NOT L39
                D IBIB ABS HITSTR L55 1-2

     FILE 'REGISTRY' ENTERED AT 08:08:01 ON 30 JUL 2009
                D STAT QUE L41
                D IDE L41 1-2

     FILE 'CAPLUS' ENTERED AT 08:08:23 ON 30 JUL 2009
                D QUE NOS L48
L56           1 SEA SPE=ON  ABB=ON  L48 NOT L39
                D IBIB ABS HITIND

     FILE 'REGISTRY' ENTERED AT 08:08:54 ON 30 JUL 2009
                D QUE L45

     FILE 'CAPLUS' ENTERED AT 08:09:05 ON 30 JUL 2009
                D QUE L50
                D IBIB ABS HITSTR L50 74-87

     FILE 'REGISTRY' ENTERED AT 08:10:55 ON 30 JUL 2009
                D QUE L43
                D QUE L52

     FILE 'CAPLUS' ENTERED AT 08:11:17 ON 30 JUL 2009
                D QUE L53
                D IBIB ABS HITSTR L53 530-539
                D QUE L49
L57        1006 SEA SPE=ON  ABB=ON  L49 NOT L53
                D IBIB ABS HITSTR L57 997-1006
                D STAT QUE L10

=>
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